BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
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Division / Office	DVRPA/OVRR
Priority Review	No
Reviewer Name	Cynthia Nolletti, MD
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Applicant	bioCSL Pty Ltd
Established Name	Quadrivalent Influenza Vaccine
(Proposed) Trade Name	Afluria Quadrivalent
Pharmacologic Class	Vaccine
Formulation	Each 0.5mL dose contains 15µg hemagglutinin (HA), total 60µg, from each of the recommended influenza types and subtypes: • A/H1N1 • A/H3N2 • B/Yamagata • B/Victoria The multidose vial also contains thimerosal (24.5mcg mercury per 0.5mL dose).
Dosage Form and Route of Administration	Sterile suspension for intramuscular (IM) injection supplied in single dose 0.5mL pre-filled syringes and 5mL multidose vials (ten 0.5mL doses).
Dosing Regimen	One 0.5mL dose IM by needle-syringe (adults ≥18 years) or PharmaJet Stratis Needle-Free Injection System (adults 18 through 64 years).
Indication and Intended	Active immunization against influenza

Population	disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. Adults ≥18 years.
Orphan Designated	No

TABLE OF CONTENTS

GLOSSARY

ACIP	Advisory Committee for Immunization Practices
AE	adverse event
AESI	adverse event of special interest
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	complete study report
DSMB	data safety monitoring board
EP	Evaluable Population
ES	Executive Summary
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act of 2007
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IIV	inactivated influenza vaccine
IIV3	trivalent inactivated influenza vaccine
IIV4	quadrivalent inactivated influenza vaccine
IM	intramuscular
ISE	integrated summary of efficacy
ITT	intent-to-treat
JI	jet injector
LAIV	live attenuated influenza vaccine
LB	lower bound
MAE	medically attended event
mcg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NA	neuraminidase
NH	northern hemisphere
NI	non-inferiority
OBE	Office of Biostatistics and Epidemiology
OBE/DE	Office of Biostatistics and Epidemiology/Division of Epidemiology
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PMC	postmarketing commitment
PMR	postmarketing requirement
PPP	Per Protocol Population
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan

PVP	Pharmacovigilance Plan
PT	Preferred Term
QIV	quadrivalent influenza vaccine
REMS	risk evaluation and mitigation strategy
RIV	recombinant influenza vaccine
RNA	ribonucleic acid
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SCR	seroconversion rate
SH	southern hemisphere
SOC	system organ class
SP	Safety Population
TEAE	treatment emergent adverse event
TIV	trivalent influenza vaccine
VAERS	Vaccine Adverse Event Reporting System
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System
VRBPAC	Vaccine and Related Biologics Products Advisory Committee
UB	upper bound

1. Executive Summary

Afluria Quadrivalent (also referred to as “Afluria QIV” in this review) is an inactivated, split virion quadrivalent influenza vaccine (QIV) indicated for active immunization against influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine, for use in adults 18 years and older. Afluria QIV is manufactured in eggs by the same process as Afluria Influenza Vaccine, a trivalent formulation (TIV) initially approved on September 28, 2007 and currently licensed for use in persons 5 years and older. Unlike the trivalent formulation, Afluria QIV contains two B virus strains, one from each of two phylogenetic lineages. Quadrivalent influenza vaccines mitigate the potential for antigenic mismatch and poor efficacy associated with an incorrect prediction of which B lineage virus will predominate in any given season. The dosage of Afluria QIV in adults is 60mcg [15mcg per hemagglutinin (HA) antigen] administered intramuscularly (IM).

BioCSL (also referred to as “the Applicant” in this review, and, as of April 15, 2016, now identified as Seqirus Pty Ltd) submitted data from a single study, CSLCT-QIV-13-01, to support the safety and effectiveness of Afluria QIV in adults 18 years and older. CSLCT-QIV-13-01 was a prospective, phase 3, observer-blind, comparator-controlled, multicenter study conducted in the U.S. during the Northern Hemisphere (NH) 2014-2015 influenza season in 3484 healthy adults ≥18 years, stratified by age (18 through 64 years and ≥65 years), and randomized 2:1:1 to receive Afluria QIV, U.S.-licensed 2014-2015 Afluria TIV-1 (Afluria), or Afluria TIV-2 containing the alternate B virus strain. Immune responses to the study vaccines were measured by hemagglutination inhibition (HI) antibody titers to each of the influenza virus antigens contained in the study vaccines, collected prior to vaccination on Day 0 and again 21 days post-vaccination. HI titers are currently the best available surrogate marker of activity reasonably likely to predict clinical benefit. The non-inferiority (NI) analyses and success criteria used in this study are recommended by CBER and are typically used in the evaluation of effectiveness of influenza vaccines by immunogenicity. Safety was evaluated by active solicitation of local and systemic symptoms and temperature for 7 days post-vaccination

(Day 1 through Day 7), and passive recording of unsolicited adverse events (AEs) and concomitant medications for 28 days post-vaccination, on diary cards. Cellulitis-like reactions, cellulitis, and Grade 3 induration/swelling at the injection site were of interest and monitored for 28 days post-vaccination. Serious adverse events (SAEs) and adverse events of special interest (AESIs), defined as medically significant events associated with the pharmacologic class of influenza vaccines, were monitored for 180 days post-vaccination.

The primary objective of the study was to demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of Afluria TIV containing the same virus strains as the U.S.-licensed 2014-2015 Seqirus influenza vaccine (Afluria TIV-1), and the TIV containing the alternate B strain (Afluria TIV-2) among adults aged ≥18 years. The study was powered to demonstrate the non-inferior immunogenicity of Afluria QIV as compared to Afluria TIV-1 and TIV-2 in two age strata, adults 18 through 64 years and ≥65 years, as a secondary objective. Other secondary objectives were to demonstrate the immunological superiority of Afluria QIV compared to Afluria TIV-1 and TIV-2 for the B strain that was not included in each TIV vaccine separately, and to assess the reactogenicity and safety of Afluria QIV.

CSLCT-QIV-13-01 pre-specified eight co-primary endpoints of Day 21 HI geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences for each of four vaccine virus strains for the immunogenicity population comprised of both age groups. Seroconversion was defined as achieving a 4-fold increase in post-immunization HI titer from a baseline of ≥ 1:10, or a post-immunization HI titer of ≥1:40 when the baseline was < 1:10. Non-inferior immunogenicity of Afluria QIV as compared to Afluria TIV-1 and Afluria TIV-2 was demonstrated if, for each of the four vaccine virus strains:

- The upper bound (UB) of the two-sided 95% confidence interval (CI) for the GMT ratio (GMT Afluria TIV / GMT Afluria QIV) was ≤ 1.5, *AND*
- The UB of the two-sided 95% CI for the SCR difference (SCR Afluria TIV – SCR Afluria QIV) was ≤ 10%.

Secondary immunogenicity endpoints included the NI of Afluria QIV compared to Afluria TIV-1 and Afluria TIV-2 assessed separately within each age group (18 through 64 years and ≥ 65 years) as described for the primary endpoint, and the immunological superiority of the alternate B strain (e.g., the influenza B strain included in the QIV but not in the TIV formulation). Immunological superiority of the alternate B strain was defined as a lower bound (LB) of the 95% CI for the GMT ratio of Afluria QIV / Afluria TIV > 1.0 and a LB of the 95% CI for the SCR difference Afluria QIV – Afluria TIV > 0.

Secondary safety endpoints included the incidence and severity of solicited injection site reactions and systemic symptoms in the seven days post-vaccination; unsolicited AEs in the 28 days post-vaccination; Grade 3 induration/swelling, cellulitis, or cellulitis-like reactions at the injection site in the 28 days post-vaccination; and SAEs in the six months post-vaccination.

Summary of Immunogenicity

The Per Protocol Population (PPP) was used for the primary and secondary immunogenicity analyses and included a total of 3395 subjects, 1691 of whom received Afluria QIV, 854 Afluria TIV-1, and 850 Afluria TIV-2. Afluria QIV elicited immune responses that met all eight pre-specified co-primary endpoints of GMT ratios and SCR differences for the four vaccine antigens required to demonstrate NI to the Afluria

comparator TIV vaccines in adults ≥18 years of age. Afluria QIV also met all co-secondary endpoints of GMT ratios and SCR differences for each antigen within each age stratum of subjects 18-64 years and ≥65 years, demonstrating NI to the TIV comparators in each age group with 80% statistical power. Finally, Afluria QIV met secondary HI GMT and SCR endpoints and pre-specified criteria for superior GMT ratios and SCR differences for each B strain as compared to U.S.-licensed Afluria TIV-1 and TIV-2 containing the alternate B strain, demonstrating immunological superiority against the alternate B strains within both age cohorts 18-64 years and ≥65 years and overall. Table 1 presents the results of the primary endpoint analyses for adults ≥18 years of age:

Table 1: Analyses of Non-inferiority, GMT ratios and SCR differences, of Afluria QIV Relative to Afluria TIV 21 Days Post-vaccination in Adults ≥18 Years (Per Protocol Population) – CSLCT-QIV-13-01

Strain	QIV GMT[1] (n=1691)	Pooled TIV or TIV-1 or TIV-2 GMT (n=1704)[2]	GMT ratio (95%CI)[3]	QIV SCR[4] (n=1691)	Pooled TIV or TIV-1 or TIV-2 SCR (n=1704)[2]	SCR Difference (95%CI)[5]	Met both NI criteria?[6]
A/H1N1	302.1	281.1	0.93 (0.88,0.99)	38.8	37.7	-1.1 (-4.5,2.3)	Yes
A/H3N2	488.5	454.5	0.93 (0.88,0.98)	40.9	39.3	-1.7 (-5.0,1.7)	Yes
B/YAM	64.1	56.0	0.87 (0.82,0.93)	31.0	27.8	-3.2 (-7.4,0.9)	Yes
B/VIC	87.6	83.0	0.95 (0.88,1.03)	40.3	38.7	-1.6 (-5.8,2.5)	Yes

Source: STN 125254/565.12, Module 5, CSLCT-13-01 CSR, Tables 11.4-1, 14.2.1.1, and 14.2.2.1.1 (30May2016)
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; AH3N2=A/Texas/50/2012 (H3N2)-like virus; B/YAM=B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC=B/Brisbane/60/2008-like virus (B/Victoria lineage); QIV=Afluria QIV; TIV-1=Afluria TIV-1 containing B/Yamagata; TIV-2=Afluria TIV-2 containing B/Victoria; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval, NI=non-inferiority.
[1]GMTs adjusted for covariates: treatment group, age subgroup, sex, vaccination history, pre-vaccination GMT, and investigator site.
[2]TIV-1 and TIV-2 are pooled for the A strain analyses, (n=1704). TIV-1 (B/Yamagata), n=854. TIV-2 (B/Victoria), n=850.
[3]GMT ratio=Afluria TIV over Afluria QIV. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[4]SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
[5]SCR difference=Afluria TIV SCR minus Afluria QIV SCR. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[6]Non-inferiority criteria for GMT ratio: upper bound (UB) of the two-sided 95% CI on the ratio of pooled TIV or TIV-1 or TIV-2 / Afluria QIV should not exceed 1.5. NI criteria for SCR difference: UB of the two-sided 95% CI on the difference between SCR pooled TIV or TIV-1 or TIV-2 – Afluria QIV should not exceed 10%.

Secondary immunogenicity endpoints of post-vaccination GMTs, proportions of subjects with post-vaccination HI titers ≥1:40, and SCRs showed that immune responses were similar between Afluria QIV and the two TIV comparators, overall and within each age cohort. However, as has been observed in other influenza vaccine studies, SCRs to all vaccine virus strains were statistically significantly lower in adults ≥65 years of age as compared to the younger age cohort.

Summary of Safety

Six subjects died during the study, five in the Afluria QIV group and one in the Afluria TIV-2 group. None of the deaths appeared related to study vaccines.

A total of 89 SAEs (including deaths) were experienced by 66 subjects during the six month safety follow-up period. Of these, 15 SAEs occurred in 12 subjects within the 28 days post-vaccination. Overall, more recipients of Afluria QIV reported SAEs as compared to recipients of TIV-1 or TIV-2 (2.3% versus 1.6%, and 1.5%, respectively), and more subjects in the older age cohort ≥65 years experienced SAEs as compared to younger adults 18-64 years of age (3.0% versus 0.8%). No specific SAE or group of events categorized either by MedDRA PT or SOC occurred with a frequency of ≥1%, and no specific imbalance or pattern was observed across treatment groups. The majority of SAEs appeared unrelated to the study vaccines due to a lack of a strong temporal relationship, lack of biological plausibility, and/or an alternative causal explanation.

Overall, a total of 37.4% of subjects experienced solicited local adverse reactions after vaccination with Afluria QIV as compared to similar rates following TIV-1 (34.6%) or TIV-2 (36.6%). More adults 18-64 years of age reported solicited local adverse reactions as compared to adults ≥65 years of age (48.4% vs 26.6%). In both age cohorts pain was the most common injection site reaction. Slightly higher proportions of Afluria QIV recipients reported measured injection site erythema (4.2% vs 2.1%-2.5%) and induration (3.2% vs 1.6%-1.8%) as compared to recipients of TIV-1 and TIV-2, but rates were low overall. Most local reactions were mild to moderate in severity, with <1% reported as severe across age and treatment groups. The majority of local reactions resolved within two to three days.

Overall, a total of 28.9% of subjects experienced solicited systemic AEs after vaccination with Afluria QIV as compared to similar rates following TIV-1 (28.4%) or TIV-2 (27.2%). More adults 18-64 years of age reported solicited systemic adverse events following Afluria QIV as compared to adults ≥65 years of age (38.3% vs 19.7%). The most common events across both age cohorts (>10%) were muscle ache/myalgia and headache. Fever was uncommon, 0.5%-0.9% across treatment and age groups. Most solicited systemic events were mild to moderate in severity, with 2.0% of all subjects experiencing severe symptoms. No large imbalances were noted across treatment groups. The majority of systemic symptoms resolved within one to two days.

Overall, rates, severity, and duration of local and systemic solicited AEs were similar between the quadrivalent and trivalent formulations and were not unusual for an inactivated influenza vaccine.

Due to concerns for a potential increase in local reactogenicity with the addition of a second B strain antigen relative to the trivalent formulation, which had increased reports of local cellulitis reactions during the 2011-2012 Northern Hemisphere season, monitoring of severe (Grade 3) induration/swelling, cellulitis-like reactions, and cellulitis at the injection site were pre-specified safety endpoints in CSLCT-QIV-13-01. Although the total number of subjects who experienced Grade 3 injection site induration/swelling in the study was relatively low (n=6/3449, 0.17%), there was a clear imbalance between severe injection site swelling in subjects treated with Afluria QIV (0.3%) as compared to recipients of Afluria TIV-1 or TIV-2 (0.06%). Whether this was due to chance alone or to greater reactogenicity caused by an additional B strain antigen is not known. Four of the six severe injection site swelling reactions occurred in subjects ≥65 years (in contrast to the overall lower rates of local reactogenicity in this age cohort). None were serious. Cellulitis and large injection site swelling are described in Section 6.2 of the Package

Insert. Postmarketing surveillance for such reactions will continue following approval of Afluria QIV.

A total of 719 subjects (20.8%) reported 1343 spontaneous or unsolicited AEs in the 28 days following vaccination, with similar proportions across treatment groups and age cohorts. Frequencies of individual events were low and similar across treatment groups and between age cohorts. The most common unsolicited AEs overall were headache (3.5%), oropharyngeal pain (1.8%), and back pain (1.7%). No large imbalances or unusual patterns were observed. Most events were mild to moderate in severity and appeared unrelated to study vaccine.

PREA Considerations

Afluria QIV triggered the Pediatric Research Equity Act (PREA) because it contains a new active ingredient (a second influenza type B virus antigen). Accordingly, the submission included a Pediatric Study Plan (PSP) and requests for a partial waiver and deferral of pediatric studies. Studies in children from birth to < 6 months of age will be waived because Afluria QIV does not represent meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in a substantial number of infants younger than 6 months. Assessments in two pediatric age groups are deferred because the product is ready for approval for use in adults, and pediatric studies have not been completed. The Pediatric Research Committee (PeRC) agreed with the Applicant's PSP on February 10, 2016. Table 2 presents the two phase 3 pediatric postmarketing requirements (PMRs) and their associated timelines:

Table 2: Afluria Quadrivalent Pediatric Postmarketing Requirements (PMRs)

Study/Age Group	Final Protocol Submission	Study Completion Date	Final Report Submission
CSLCT-QIV-13-02 5 yrs through 17 yrs	July 31, 2015	June 30, 2016	December 31, 2016
CSLCT-QIV-13-03 6 mos through 4 yrs	July 31, 2016	June 30, 2017	December 31, 2017

Source: Adapted from STN 125254/565, Module 1, Section 1.9.2, Request for Deferral of Pediatric Studies.

Pharmacovigilance Plan – PMCs, PMRs

The Applicant will continue routine monitoring of severe reactogenicity, other identified risks (hypersensitivity and anaphylaxis), and potential risks associated with influenza vaccination (encephalomyelitis, seizures/convulsions, Guillain-Barre syndrome, transverse myelitis, optic neuritis, Bell's palsy, and serum sickness). Additionally, exposure, safety, and outcomes in pregnancy will be assessed by a pregnancy registry, a prospective observational study of pregnant women exposed to Afluria QIV (protocol to be reviewed by OBE/DE). OBE/DE does not recommend a PMR designed specifically to evaluate safety as a primary endpoint, a risk evaluation and mitigation strategy (REMS), or a Black Box warning for administration of Afluria QIV. The clinical review team agreed with the OBE/DE recommendation. Please see the OBE/DE review for a full discussion of the PVP, PREA Considerations of this section, and Section 9.1.3 for further discussion of pediatric PMRs.

Recommendation based on Risk Benefit

From the clinical perspective, the safety and immunogenicity data from CSLCT-QIV-13-01 support a recommendation for traditional approval of Afluria QIV in adults ≥18 years of age.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

This efficacy supplement consisted of one clinical trial comparing the safety and immunogenicity of Afluria QIV to two trivalent formulations manufactured by Seqirus containing B antigens from different lineages. The distribution of demographic and baseline characteristics was similar among all three treatment groups in the full analysis set (FAS) population (all 3484 volunteers 18 years of age and older who provided informed consent and were randomized to receive study treatment). Overall, there were more female (57.2%) than male (42.8%) subjects. The majority of subjects were white (82.3%) and non-Hispanic or Latino (94.9%). Black/African American and Hispanic/Latino subjects comprised 15.8% and 4.9% of the FAS, respectively, while other racial groups were each <1% of the population. Baseline characteristics were also similar between age groups with the exception of a higher proportion of black/African American subjects in the 18-64 years age group (25.5%) as compared to the ≥65 years age group (6.0%). Relative to the US population (July 2014 US census data), females and whites were overrepresented and Hispanics/Latinos underrepresented. Blacks and African Americans were overrepresented in the younger age cohort and underrepresented in the ≥65 years age cohort.

The mean age of all subjects in the FAS was 58.3 years [standard deviation (SD) 18.04]; 43.5 years (SD13.48) in the 18-64 years age group; and 73.1 years (SD 5.59) in the ≥ 65 years age group. The proportions of subjects in age subgroups were as follows: 18-49 years (29.3%); 50-64 years (20.7%); 65-74 years (31.1%); and ≥75 years (19.0%).

Subpopulation analyses revealed a tendency for females to report more solicited and unsolicited adverse events as compared to males. Females reported more solicited AEs overall as compared to males (52.7% versus 37.3%), driven primarily by injection site pain (39.8% vs 29.2%), headache (17.0% vs 9.0%), myalgia (20.6% vs 16.3%), and malaise (8.1% vs 5.2%). A higher proportion of females also reported unsolicited AEs as compared to males (23.5% versus 17.1%, respectively, overall), driven primarily by headache (4.4% vs 2.3%) and diarrhea (2.0% vs 0.6%). No large differences in the severity or relatedness of unsolicited AEs were observed between the sexes. Immune responses in males and females following vaccination were similar. Due to small sample sizes, there was insufficient information to draw definitive conclusions about effectiveness or safety in racial or ethnic subgroups. However, sub-analyses showed trends towards lower rates of solicited local injection site reactions in blacks and African Americans as compared to whites, and more solicited local and systemic reactogenicity among Hispanics and Latinos as compared to non-Hispanics or Latinos.

2. Clinical and Regulatory Background

On September 28, 2007, Afluria (Seqirus's trivalent split virion inactivated influenza vaccine) was approved for active immunization against influenza disease caused by influenza A subtype viruses and the type B virus contained in the vaccine in adults 18 years of age and older. The indication has since been extended to persons 5 years of age and older. Dosage of the trivalent formulation in adults is 45 µg [15 µg of HA antigen per virus strain] administered IM. In this efficacy supplement, the Applicant has submitted safety and immunogenicity data to support an indication for a new quadrivalent formulation containing two type B virus strains, representing both B virus genetic lineages (Yamagata and Victoria), for use in adults ≥18 years of age.

2.1 Disease or Health-Related Condition(s) Studied

Influenza is an important infectious cause of death in the U.S. and throughout the world, with influenza-associated respiratory and circulatory mortality rates ranging from 3,349 to 48,614 in the U.S. from 1976 to 2007 (average annual mortality of 23,607) and 250,000 to 500,000 deaths worldwide each year. It is responsible for more deaths in the U.S. than all other vaccine-preventable diseases combined. In seasons when influenza A/H3N2 predominates, mortality has been 2.7 times higher than when other strains (A/H1N1 or B) have predominated. A Centers for Disease Control and Prevention (CDC) study covering the period 1990-1999, during which A/H3N2 predominated in the U.S., estimated an annual average mortality of 36,155. During seasonal influenza epidemics in the U.S. from 1979-2001, the CDC estimated that influenza-associated hospitalizations ranged from 55,000 to 431,000 per season. Complications, hospitalizations and deaths from seasonal influenza disproportionately affect persons ≥ 65 years, children < 5 years (especially those < 2 years), and persons of any age with certain underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. [4,7,8,9,10,11,13,14,16,52]

Influenza is caused by RNA viruses of the family Orthomyxoviridae. Two types, influenza A and B, cause the vast majority of human disease. Influenza A is further categorized into subtypes based on two principal surface antigens, hemagglutinin (HA) and neuraminidase (NA), which comprise the viral glycoprotein coat. There are multiple subtypes of Influenza A based on combinations of 18 variants of HA and 11 variants of NA, but only subtypes H1N1, H2N2, and H3N2 appear to circulate in humans. Influenza A has also been isolated from non-human species including birds, horses, and swine. In contrast to influenza A, influenza B is comprised of single HA and NA subtypes, and is only known to occur in humans. Antibodies to influenza surface antigens are subtype and strain-specific, and confer protection against future infection with identical strains, but not against another type or subtype. Historically, the A/H3N2 strain has been associated with a higher mortality rate as compared to the A/H1N1 or B strains, although the B strain is known to cause serious disease in children. [8,9,26]

Although influenza B viruses are not categorized into subtype based on HA and NA, they are divided into two distinct genetic lineages (Yamagata and Victoria) which have co-circulated since 1985 and together comprise approximately 25% of all positive influenza specimens in the U.S. Prior to the availability of quadrivalent influenza vaccines, trivalent vaccines contained only one B virus antigen representing one lineage. During the ten seasons from 2001-2002 through 2010-2011, public health agencies were only able to correctly predict the predominant B lineage in five seasons, resulting in a mismatch between the vaccine and circulating strains for half of the 10 year period. The CDC estimated that in a season where there is a B strain mismatch, the availability of a quadrivalent vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths. In recent years, rates of hospitalization and mortality attributed to influenza B virus have been recognized as being lower than A/H3N2 but higher than A/H1N1, and, overall, similar to those attributed to seasonal influenza A viruses. The CDC estimates that 80%-90% of seasonal influenza-related deaths and 50%-70% of hospitalizations occur in adults ≥65 years. Thus, the disease burden of influenza B infections in the elderly is substantial. Vaccine coverage of both B strains is also desirable in young children who experience disproportionately high mortality due to B strains. Although influenza B causes ~25% of all clinical disease, 34% of the 309 pediatric deaths reported to the CDC during 2004-

2008 and 38% of 115 pediatric deaths reported during the 2010-2011 season were due to influenza B. One case series of autopsies on patients with fatal influenza B infections (including 32 mostly healthy children <18 years) demonstrated that the influenza B infections were severe, rapidly progressive, and that 69% of 29 cases with available cardiac tissue were associated with myocardial injury. The authors also observed an age-related difference in complications of influenza B disease. While 82% of deaths in adults ≥18 years were associated with bacterial superinfection, most (90%) of the influenza B deaths in children <18 years were associated with myocardial injury. In 2013, the World Health Organization (WHO) and the VRBPAC recommended the inclusion of a second influenza B vaccine virus antigen in quadrivalent influenza vaccines to provide coverage of both B lineages. Since the NH 2013-2014 influenza season, five quadrivalent influenza vaccines have been licensed for use in the US. It is expected that, over time, quadrivalent formulations will become the standard of care for influenza vaccines. [3,11, 34,46, 49]

Since 1977, influenza A subtypes H1N1 and H3N2 and influenza B have co-circulated globally. Seasonal epidemics generally occur during the winter months and are caused by antigenic drift, new antigenic variants or viral strains that result from point mutations in the viral genome that occur during replication. Antigenic variants or strain changes occur each year necessitating annual change in the formulation of influenza vaccines for optimal protection. Neutralizing antibody against HA is the primary immune defense against infection with influenza. Although there is no established absolute immune correlate of protection, studies have suggested that HI titers of 1:32 to 1:40 correlate with protection against illness. This strain-specific immune response appears to predict a clinical endpoint of efficacy with reasonable certainty. Previous experience with inactivated influenza vaccines supports use of HI titers as a surrogate endpoint. [8,9,22,26,27,28,31]

The primary mode of controlling influenza disease is immunoprophylaxis. Because of the potential for serious and life-threatening influenza-related disease, the CDC's Advisory Committee on Immunization Practices (ACIP) has, over the last decade, broadened its recommendations for immunoprophylaxis of influenza and now recommends influenza vaccination for all persons 6 months of age and older without known contraindications. [8,11,14]

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Five licensed antiviral agents are available in the U.S. for the prevention or treatment of influenza in persons with confirmed or suspected severe, complicated, or progressive influenza, or in those at higher risk for complications. Treatment of persons without known risk factors may also be considered if treatment can be initiated within 48 hours of onset or if infection with a novel influenza virus is suspected. Two older adamantane agents, amantadine and rimantidine, are active only against influenza A and are no longer recommended because of widespread resistance since 2005. One of three neuraminidase (NA) inhibitors, oseltamivir is an oral antiviral indicated for the treatment of influenza A and B in persons ≥ 14 days of age and for chemoprophylaxis in persons ≥1 year of age. Frequent gastrointestinal side effects may limit its usefulness. Emergence of resistance during treatment with oseltamivir was a problem for seasonal H1N1viruses prior to their replacement by the 2009 pandemic H1N1 strains which are now in circulation and only rarely resistant. Currently, seasonal H3N2 and B strains are

also rarely resistant to oseltamivir. Zanamivir, another NA inhibitor, is indicated for chemoprophylaxis of influenza in persons ≥ 5 years of age and for treatment in persons ≥ 7 years of age. It is administered as an orally inhaled powder and is associated with bronchospasm especially in persons with underlying asthma or chronic obstructive pulmonary disease. It is rarely associated with resistance. The third and newest NA inhibitor, peramivir, is a single dose intravenous antiviral indicated only for the treatment of uncomplicated influenza A and B viral infection in persons 18 years of age and older. Adverse events include diarrhea, serious cutaneous reactions and postmarketing reports of neuropsychiatric events. Due to concerns for potential emergence of resistance and side effects, NA inhibitors are considered important adjuncts but not substitutes for vaccination. [10,11,14,19,26]

2.3 Safety and Efficacy of Pharmacologically Related Products

Licensed influenza vaccines available in the United States include: trivalent and quadrivalent inactivated influenza vaccines (IIV3 and IIV4), a trivalent recombinant influenza vaccine (RIV3), live-attenuated influenza vaccines (LAIV), and, more recently, one high dose and one adjuvanted trivalent inactivated vaccine. These vaccines are grown either in egg or cell culture. Six IIV3 (Afluria, Fluarix, FluLaval, Fluviron, Fluzone, and Flucelvax) and three IIV4 (Fluarix, FluLaval, and Fluzone) standard dose (15 mcg HA per antigen) vaccines are licensed for use in the US in adults 18 years of age and older. A fourth IIV4 (Fluzone Intradermal) is limited to use in adults 18-64 years of age. One RIV3 (Flublok) is approved for use in adults 18 years and older. LAIV (FluMist Quadrivalent) is currently approved for use only in healthy non-pregnant persons 2 to 49 years of age. When vaccine and circulating viruses are antigenically well-matched, vaccination with IIV3 has been estimated as 70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. These estimates are limited by a relative lack of randomized placebo-controlled trials and limitations associated with test negative case control observational designs. Effectiveness is lower among persons with underlying illnesses, those ≥ 65 years of age, or when there is a poor antigenic match between vaccine and circulating influenza virus strains. Because of lower immune responses observed in the elderly, two other trivalent inactivated influenza vaccines with improved immunogenicity over standard IIVs were developed and licensed for use in adults ≥65 years of age: Fluzone High Dose (45 mcg HA per antigen) and Fluad [the first U.S.-licensed IIV3 (Agriflu) formulated with an adjuvant (MF59)].
[8,12,13,14,15,16,18,20,21,23,27,30,32,33,36,37,38,40,41,42,43,45,47,48,50,53,57]

Seasonal inactivated influenza vaccines (IIV) licensed for use in the U.S. have a long history of safety. The most common adverse events (AEs) associated with IIVs are local injection site reactions, e.g., pain, erythema, and induration. These reactions generally occur in >10% of patients, are usually mild to moderate in intensity, and are relatively short in duration (24-48 hours). Systemic symptoms following vaccination, e.g., fever, arthralgia, myalgia, headache, are less common and, in randomized controlled trials, often occur at rates similar to those observed in placebo recipients making causality less certain than local reactions. [13,26,29,51,56]

Uncommon or rare AEs associated with influenza vaccines include neurologic events such as encephalitis, myelitis, and Guillain-Barre syndrome, and allergic or immediate hypersensitivity reactions, e.g., urticaria or angioedema. The incidence of anaphylaxis following IIV3 has been estimated as 1.35 cases per million doses (95% CI: 0.65, 2.47). While rare, anaphylactic reactions may occur following exposure to any component of

the vaccine, including, for example, antigen, residual animal or cell proteins, antimicrobial agents, preservatives, or stabilizers. [13,26,29,35,51,56]

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Seqirus IIV4 (Afluria Quadrivalent) has not been licensed by any other regulatory authority. However, Seqirus' IIV3 vaccine has been marketed in Australia and New Zealand since 1968 and globally since 1985. The manufacturing process has not changed since 1985 except for eliminating the preservative, thimerosal, from single use presentations in 2002. Please refer to Section 2.5 of this review, the Afluria Package Insert (PI) and the clinical reviews of STN 125254 Amendments 0, 132, and 259 for information regarding previous experience with Afluria in subjects 6 months and older.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

- September 28, 2007 – STN 125254/0. Accelerated approval was granted to Afluria for use in adults 18 years of age and older.
- November 10, 2009 – STN 125254/132. Accelerated approval was extended to children 6 months through 17 years of age during the 2009 H1N1 influenza pandemic so that a second pandemic vaccine would be available for children 6 months through 2 years of age.
- December 2, 2011 – STN 125254/259, efficacy supplement. Traditional approval granted in adults aged 18 years and older (based on fulfillment of PMCs to conduct a clinical endpoint study in adults 18 through 64 years of age and studies of non-inferior immunogenicity in adults ≥65 years of age) and in children and adolescents 5 through 17 years of age (based on fulfillment of PMCs to conduct studies of safety and non-inferior immunogenicity). Please see the clinical review for details.
- April 2013 – STN 125254/440, labeling supplement. The postmarketing section (6.2) of the Afluria PI was revised to include "cellulitis and large injection site swelling". The Applicant also committed to close monitoring of postmarketing cases of cellulitis-like injection site reactions. Please see the clinical review of data submitted to STN 125254/440.1 and 440.2 for details.
- December 2013 – IND 12297/130 – Final summary of Seqirus' scientific investigation into the root cause of postmarketing reports of increased fever and febrile seizures associated with the Southern Hemisphere (SH) 2010 formulation of Afluria that supported revision of the indications and usage of Afluria to persons 5 years of age and older on July 15, 2011 (please see the clinical review of STN 125254/181.1 for details).Based on this investigation, Seqirus [redacted] for the 2014-2015 influenza season vaccine (and for the vaccines used in study CSLCT-QIV-13-01 submitted to this sBLA).
- March 12, 2013 – A pre-IND meeting was held with bioCSL to discuss the Afluria QIV clinical development plan (CRMTS#8832; PTS#1965, IND 15974). During this meeting we offered the Applicant the option of conducting a study in adults to compare the non-inferior immunogenicity of Afluria QIV to Afluria TIV and Afluria TIV-2 containing the alternate B strain not included in the seasonal trivalent vaccine (versus using a U.S.-licensed QIV comparator). Because of concerns over the 2011 increase in reports of severe local reactogenicity and a potential increase in reactogenicity due to the addition of a second B strain, the Applicant

agreed to our request to monitor subjects for Grade 3 induration/swelling and cellulitis-like injection site reactions. Regarding pediatric studies, we agreed with the Applicant's plan to study older before younger children, and informed the Applicant that we would require a minimum safety database of 3000 children 5 through 17 years of age, weighted more heavily towards the younger age group.

- March 28, 2014 –The adult QIV protocol CSLCT-QIV-13-01 and an initial Pediatric Study Plan (iPSP) were submitted in IND 15974/0. The general investigative plan also included a proposal to conduct a small safety study (CSLCT-USF-10-69) of Afluria TIV in children 5 through 8 years of age using a [redacted] concurrent with CSLCT-QIV-13-01 and prior to conducting a larger study of Afluria QIV in children 5 through 17 years of age.
- August 8, 2014 – The Applicant submitted an agreed iPSP incorporating CBER's recommendations to IND 15974/4. See Section 9.1.3 of this review for details of the PSP.
- August 15, 2014 – STN 125254/511. CBER approved Seqirus' supplement to support the safety and efficacy of administration of Afluria by the PharmaJet® Stratis® Needle-Free Injection System (a jet injector) in persons 18 through 64 years of age.
- April 15, 2016 – CBER acknowledged the Applicant's change in name from bioCSL Pty Ltd to Seqirus Pty Ltd.
- April 21, 2015 – A pre-BLA meeting was held to discuss the submission of STN 125254/565.
- February 10, 2016 – The PeRC concurred with the final PSP submitted to STN 125254/565. Please see Section 9.1.3 for details of the PSP.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate conduct of a complete clinical review without unreasonable difficulty.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant stated that the protocol was written and conducted in compliance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, federal regulations, and local ethical and regulatory requirements. These requirements included IRB approval of the protocol and the informed consent of human subjects.

Bioresearch Monitoring (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality, conducted an inspection of four clinical study sites (285, 297, 302, and 308) selected based on numbers of subjects enrolled, prior FDA inspection history, and numbers and types of AEs and protocol deviations. Inspections found no deficiencies that would preclude approval. Please see the BIMO review for details.

3.3 Financial Disclosures

The Applicant provided an FDA Form 3454 and a list of investigators for the clinical study submitted to this sBLA, and certified that they had not entered into any financial agreements with the investigators that could potentially influence the outcome of the study. The Applicant certified further that each listed investigator was required to disclose their financial interests and that no disclosable financial interests or arrangements as defined by 21CFR54.2 were reported.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

At the time the clinical review was completed, the Chemistry, Manufacturing, and Controls (CMC) review team had not identified any issues that would preclude licensure. Please see the CMC review for details.

4.2 Assay Validation

The CBER assay reviewer identified no significant deficiencies in the assay validation. Please see the HI assay review for details.

4.3 Nonclinical Pharmacology/Toxicology

The review team expected the safety profile for Afluria QIV to be similar to the trivalent formulation because it is manufactured by the same process and differs only in an additional B strain. Therefore, at the March 12, 2014 pre-IND meeting, CBER informed the Applicant that no new non-clinical or toxicology data were required to support this efficacy supplement. Please refer to the meeting summary for details.

4.4 Clinical Pharmacology

Not applicable.

4.4.1 Mechanism of Action

Vaccination with inactivated influenza vaccines induces antibody responses primarily against HA and NA. Strain-specific neutralizing antibodies against HA provide the main protection against infection and clinical disease. The anti-HA antibody response, measured by the hemagglutination inhibition (HI) assay, is currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. To date, prospective studies have not identified a validated specific HI titer associated with protection against culture confirmed influenza illness. Some studies have shown that HI titers ranging from 1:32 to 1:40 are associated with protection from illness in approximately 50% of subjects and that protection from illness generally correlates with higher titers. However, no single HI titer has been identified that predicts protection. Other antibody, e.g., to NA, nuclear protein (NP), and/or M1 protein, and cellular responses to vaccination may contribute to protection. [8,9,22,24,26,27,28,31,39]

4.4.2 Human Pharmacodynamics (PD)

Not applicable.

4.4.3 Human Pharmacokinetics (PK)

Not applicable.

4.5 Statistical

Please see the statistical review. At the time the clinical review was completed, the statistical reviewer had not identified any issues that would preclude approval of the supplement.

4.6 Pharmacovigilance

Please see the OBE/DE review of the PVP. The OBE/DE reviewer identified no safety concerns that would require a PMR designed specifically to evaluate a safety endpoint and did not recommend a REMS as necessary for Afluria QIV. The Applicant agreed to establish a pregnancy registry for Afluria QIV during the pre-sBLA meeting and submitted a pregnancy registry protocol to amendment STN 125254.565.7. Please see the OBE/DE review for comment.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Seqirus conducted one pivotal study, CSLCT-QIV-13-01, to support initial licensure of Afluria QIV. The reviewer evaluated the study data for consistency with information included in the proposed PI. Study designs, endpoints, and statistical methods used in CSLCT-QIV-13-01 were very similar to those which supported licensure of Afluria (TIV). Non-inferior immune responses elicited by Afluria QIV as compared to Afluria (TIV) were considered adequate to infer clinical benefit based on the clinical endpoint data that supported licensure of Afluria (TIV) in adults 18 years and older. Because the vaccines are manufactured by the same process and have overlapping compositions, the clinical efficacy data for Afluria (TIV) are relevant to Afluria QIV and were included in the proposed PI.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN 125254/565.0 – Modules 1, 2, and 5 and associated electronic datasets.
- STN 125254/565.1 – Response to a December15, 2015 request for information.
- STN 124254/565.7 – Pregnancy registry.
- STN 125254/565.12 – Response to statistical request to recalculate the primary analyses according to the Statistical Analysis Plan.
- STN 125254/565.15 – Confirmation of PMC and PMRs.
- STN 124254/565.17 – Response to June 28, 2016 IR, revised unsolicited AEs.

5.3 Table of Studies/Clinical Trials

Table 3 presents the characteristics of the single clinical study submitted to support licensure of Afluria QIV in adults 18 years and older.

Table 3: Summary of Clinical Trials Submitted to STN 125254/565

Study ID NCT# Season Location	Design	Population Enrolled	Objectives	Endpoints*	Analysis Populations
CSLCT-QIV-13-01 NCT 02214225 NH 2014-2015 USA	Phase 3, observer-blind, comparator-controlled, multicenter, stratified by age (18-64 and ≥65 years), randomized 2:1:1 to receive a single 0.5mL IM dose of Afluria QIV, US-licensed Afluria (TIV-1, B/Yamagata), or TIV-2 (alternate B/Victoria). 0.5 mL dose = 15 mcg HA per strain	Healthy adults ≥18 years 3484 total 1741 QIV 871 TIV-1 872 TIV-2	Non-inferior immunogenicity; superiority of alternate B strains Safety	Co-primary: GMT ratio and SCR difference for each strain. Secondary: SCRs, % HI titer ≥1:40 Frequency and severity of solicited AEs (7 days), cellulitis/cellulitis-like/Grade 3 injection site reactions (28 days), unsolicited AEs (28 days), and SAEs (180 days)	Safety: 3449 total 1721 QIV 864 TIV-1 864 TIV-2 Evaluable: 3415 total 1704 QIV 857 TIV-1 854 TIV-2

Source: Adapted from STN 125254/565, Module 5, CSLCT-QIV-13-01 CSR text and Table 14.1.1.1.
NCT=ClinicalTrials.gov identifier; NH=Northern Hemisphere; IM=intramuscular; QIV=quadrivalent influenza vaccine; TIV=trivalent influenza vaccine; HA=hemagglutinin; GMT=geometric mean titers; SCR=seroconversion rate; HI=hemagglutination inhibition; AE=adverse event; SAE=serious adverse event.
*Immunogenicity assessed at 28 days post-vaccination

5.4 Consultations

Not applicable

5.4.1 Advisory Committee Meeting

Not applicable.

5.4.2 External Consults/Collaborations

Not applicable.

5.5 Literature Reviewed

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2Belongia EA, et al. Waning vaccine protection against influenza A (H3N2) in children and older adults during a single season. Vaccine. 2015;33:246-251.

3Belshe RB, et al. Efficacy of live attenuated influenza vaccine in children against influenza B viruses by lineage and antigenic similarity. Vaccine. 2010;28:2149-56.

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5Black S, et al. Influence of Statins on Influenza Vaccine Response in Elderly Individuals. J Infect Dis 2016;213:1224-1228.

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

"A phase 3, randomized, multicenter, double-blinded study to evaluate the immunogenicity and safety of quadrivalent influenza vaccine (CSL QIV) in comparison with a US-licensed 2014-15 trivalent influenza vaccine (CSL TIV), and a trivalent influenza vaccine containing the alternate B strain (CSL TIV-2), in adults aged 18 years and above."

6.1.1 Objectives

Primary Objective
To demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of Afluria TIV containing the same virus strains as the US licensed 2014-2015 Seqirus influenza vaccine (Afluria TIV-1), and the TIV containing the alternate B strain (Afluria TIV-2) among adults ≥18 years old.
Secondary Objectives
Secondary objectives were to assess the following among adults ≥18 years old in two age strata, 18 through 64 years and ≥65 years, as well as overall:

- To demonstrate that vaccination with Afluria QIV elicits an immune response that is not inferior to that of Afluria containing the same virus as the US licensed 2014-2015 Afluria TIV-1, and Afluria TIV-2);
- To demonstrate the immunological superiority of Afluria QIV compared to Afluria TIV-1 and TIV-2 for the B strain that was not included in each TIV vaccine separately;
- To characterize the immunogenicity of Afluria QIV, Afluria TIV-1, and Afluria TIV-2;
- To assess the safety and tolerability of Afluria QIV.

6.1.2 Design Overview

CSLCT-QIV-13-01 was a phase 3, randomized, observer-blinded, comparator-controlled, multicenter study of Afluria QIV versus U.S.-licensed 2014-2015 Afluria TIV-1, and versus Afluria TIV-2, conducted during the 2014-2015 NH influenza season in healthy male and female adults 18 years and older. For each age stratum, subjects were randomized 2:1:1 to one of the three treatment groups. The randomization was stratified by age, 18 through 64 years and ≥65 years, employing a quota to ensure an equal number of subjects in each age stratum. Further substratification within each age stratum was planned for a total of four age groups: 18 through 49 years; 50 through 64 years; 65 through 74 years; and ≥75 years.

A single dose of vaccine was administered IM on Day 1. Blood samples were collected prior to vaccination and 21 days later for measurements of serum HI antibody titers to the virus strains included in the vaccines. Subjects recorded solicited local and systemic symptoms and temperature for 7 days post-vaccination (Day 1 through Day 7), and unsolicited AEs and concomitant medications for 28 days post-vaccination, on diary cards. Cellulitis-like reactions, cellulitis, and Grade 3 induration/swelling at the injection site were also monitored for 28 days post-vaccination. Serious adverse events and adverse events of special interest, defined as medically significant events associated with the pharmacologic class of influenza vaccines, were monitored for 180 days post-vaccination.

Reviewer comment: The study design was similar in design to studies supporting licensure of other quadrivalent influenza vaccines, and was agreed upon in a meeting held with the Applicant on March 12, 2013. The randomization and blinding procedures were deemed adequate by the statistical reviewer.

Reviewer comment: During the 2011-2012 NH influenza season, the Applicant's routine safety surveillance system identified increased reports of large injection site swelling and injection site cellulitis associated with the use of Afluria TIV. These events were subsequently included in the PI. During the March 12, 2013 pre-IND meeting for Afluria QIV, FDA requested monitoring of such events in the QIV development program. Thus, CSCT-QIV-13-01 pre-specified safety endpoints included the occurrence of cellulitis-like reaction, cellulitis, and Grade 3 induration/swelling at the injection site in the 28 day period post-vaccination. Although the Applicant's routine postmarketing surveillance includes monitoring and reporting of large/extensive swelling and cellulitis-like injection site reactions to FDA, the Applicant does not specifically categorize these events as AESIs or include them in the formal Pharmacovigilance Plan (PVP). We have asked OBE/DE to comment on whether it is appropriate to add these events to the formal PVP. Please see the OBE/DE review for further discussion.

6.1.3 Population

Selected Inclusion Criteria

- Healthy male or non-pregnant female (as determined by negative urine pregnancy test immediately prior to vaccination) ≥ 18 years of age
- Females of child-bearing potential must be abstinent or willing to use medically acceptable contraception through the Day 21 Exit Visit

Selected Exclusion Criteria

- Known hypersensitivity to previous influenza vaccination, eggs, chicken protein, or any component of the Seqirus vaccines
- Vaccination against influenza in the previous 6 months
- Receipt or plans to receive licensed vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to administration of Seqirus study vaccine, or during the 28 day post-vaccination period
- Use or planned use of an investigational product 30 days prior to and 30 days after vaccination with Seqirus study vaccine
- Clinical signs of active infection and/or oral temperature of ≥100.4°F
- History of Guillain Barre Syndrome, neurologic or seizure disorders, immunosuppressive disorders or therapy, or malignancy (topical or inhaled corticosteroids allowed)
- Any acute or unstable chronic medical condition (e.g., requiring hospitalization, significant organ function deterioration, major changes to treatment doses, or requiring major new treatment)

6.1.4 Study Treatments or Agents Mandated by the Protocol

Study Vaccine

Afluria QIV: a single 0.5 mL dose containing 15mcg of HA antigen for each of the 4 strains recommended for the NH 2014-2015 influenza season (total HA = 60mcg), administered IM into the deltoid region of the arm.

The four influenza strains recommended by FDA's VRBPAC for the NH 2014-2015 season quadrivalent vaccines were:

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Texas/50/2012 (H3N2)-like virus;
- B/Massachusetts/2/2012-like virus [B/Yamagata lineage, recommended for TIV];
- B/Brisbane/60/2008-like virus [B/Victoria lineage, alternate B strain included in QIV]

Lot Number: 090403201

Comparator Vaccines
Afluria TIV-1: a single 0.5 mL dose administered IM into the deltoid region of the arm, containing 15mcg HA for each of the 3 strains recommended for the NH 2014-2015 influenza season (total HA = 45mcg):

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Texas/50/2012 (H3N2)-like virus;
- B/Massachusetts/2/2012-like virus [B/Yamagata lineage, recommended for TIV];

Batch Number: 090401201

Afluria TIV-2: a single 0.5 mL dose administered IM into the deltoid region of the arm, containing 15mcg HA for each of the 2 influenza A strains recommended for the NH 2014-2015 influenza season and the alternate B strain (total HA = 45mcg):

- A/California/7/2009 (H1N1)pdm09-like virus
- A/Texas/50/2012 (H3N2)-like virus;
- B/Brisbane/60/2008-like virus [B/Victoria lineage, alternate B strain]

Batch Number: 090402201

Excipients (for all three study vaccines)
Sodium chloride, sodium phosphate, potassium chloride, potassium phosphate, calcium chloride, and residual amounts of TDOC, ovalbumin, sucrose, neomycin, polymyxin B, and beta-propiolactone.

All study vaccines were supplied in 0.5mL single dose pre-filled thimerosal-free syringes.

Reviewer comment: The integrated summary of efficacy (ISE), p.3, contained incorrect information indicating that Seqirus QIV contained thimerosal while the TIV vaccines were thimerosal-free. Based on communications with the CBER CMC reviewer, all three study vaccines in study CSLCT-QIV-13-01 actually used the thimerosal-free 0.5 mL pre-filled syringe formulation.

6.1.5 Directions for Use

Not applicable.

6.1.6 Sites and Centers

CSLCT-QIV-13-01 was conducted at 31 centers across the US. John Treanor, MD, was the Principal Investigator. Study sites and investigators are presented in Table 4.

Table 4: Study Sites, Investigators, and Subjects* - CSLCT-QIV-13-01

Site	Investigator	Location	#Subjects*

Site	Investigator	Location	#Subjects*
282	William Seger, MD	Fort Worth, TX	120
283	Laurence Chu, MD	Austin, TX	116
285	Frank Eder, MD	Binghamton, NY	120
286	Lydie Hazan, MD	Los Angeles, CA	120
287	Larkin Wadsworth, MD	St. Louis, MO	132
288	Darrell Herrington, MD	San Angelo, TX	87
289	Mark Turner, MD	Meridian, ID	118
291	Stephan A. Bart, Sr., MD	Rockville, MD	87
292	Paul S. Bradley, MD	Savannah, GA	118
293	Murray A. Kimmel, DO	Melbourne, FL	116
294	Daniel H. Brune, MD	Peoria, IL	120
295	Laura L. Helman, DO	Mishakawa, IN	119
296	Randle T. Middleton, MD	Huntsville, AL	119
297	James Fulmer, MD	Jacksonville, FL	83
298	Steven Folkerth, MD	Las Vegas, NV	107
299	Carl Griffin, MD	Oklahoma City, OK	115
300	Derek Muse, MD	Salt Lake City, UT	120
301	Susann Varano, MD	Milford, CT	107
302	George Raad. MD	Charlotte, NC	131
303	James R. Clark, MD	Charlottesville, VA	120
304	Rickey D. Manning, MD	Knoxville, TN	114
305	Jonathan Wilson, DO	Winston-Salem, NC	120
306	John Rubino, MD	Raleigh, NC	131
307	Richard Mills, MD	Mt. Pleasant, SC	118
308	Bernard Grunstra, MD	Bristol, TN	110
309	Kevin D. Cannon, MD	Wilmington, NC	132
310	Michael McCartney, MD	Methuen, MA	120
311	John Kirby, MD	Jefferson City, TN	65
312	Paul Wakefield, MD	Knoxville, TN	74
313	John Treanor, MD	Rochester, NY	73
315	Darren A. Farnesi, MD	San Diego, CA	117
316	James A. Cervantes, MD	Bellevue, NE	0 (Backup site)
317	Terry L. Poling, MD	Wichita, KS	0 (Backup site)

Source: Adapted from STN 125254.565, CSLCT-QIV-13-01 CSR, Appendix 16 and electronic datasets.
*Number of subjects in the Safety Population

6.1.7 Surveillance/Monitoring

The schedule of study procedures, including safety monitoring, is presented in Table 5.

Table 5: Schedule of Procedures – CSLCT-QIV-13-01

Visit/Phone Call	**Screening**	**V1**	**Call**	**V2**	**Call**	**Call**
Study Day and Window	**D-14 to -1**	**D1**	**D7+3**	**D21+4**	**D28+4**	**D180+14**
Procedure	-	-	-	-	-	-
Invitation to participate	X	-	-	-	-	-
Informed consent	X	X	-	-	-	-
Baseline characteristics[1]	-	X	-	-	-	-
Medical history including medications	-	X	-		-	-
Physical exam[2]	-	X	-	X	-	-
Vital signs	-	X	-		-	-
Urine pregnancy test[3]	-	X	-	X	-	-
Eligibility criteria	-	X	-		-	-
Serologies	-	X	-	X	-	-
Vaccination	-	X	-		-	-
Distribute study materials	-	X	-	X	-	-

Visit/Phone Call	**Screening**	**V1**	**Call**	**V2**	**Call**	**Call**
Study Day and Window	**D-14 to -1**	**D1**	**D7+3**	**D21+4**	**D28+4**	**D180+14**
7-day solicited AE diary return/review	-		X	X	-	-
21-day unsolicited AE diary return/review	-	-	-	X	-	-
Telephone contact	-	-	X	-	X	-
ILI evaluation if applicable[4]	-	X	X	X	-	-
Review AEs including cellulitis-like reactions and concomitant meds[5]	-	X	X	X	X	-
Review of SAEs	-	X	X	X	X	X

Source: Module 5, CSLCT-QIV-13-01, CSR, Table 9.5-1, p.52.
[1]Baseline characteristics: age, sex, race, ethnicity, prior influenza vaccination history
[2]Exam on Day 1: cardiovascular, dermatological, eyes, ears, nose, throat, gastrointestinal, immunological, musculoskeletal, neurological, and respiratory systems. Exam on Day 7, if indicated, was targeted.
[3]Females of child-bearing potential only
[4]Elevated oral temperature ≥100.4°F (≥ 38.0°C), or a clear history of fever or chills, and at least one flu-like symptom (including sore throat, cough, myalgia, headache, malaise, rhinitis, otitis media, nausea, and vomiting). Nasal swabs (right and left nostrils) and throat swab collected for influenza A/B RT-PCR.
[5]In the event of a cellulitis-like reaction to vaccination, obtain a complete blood count, erythrocyte sedimentation rate, and wound culture (if tissue is broken down).

Subjects were observed for immediate hypersensitivity reactions for 30 minutes post-vaccination.

Subjects were instructed to contact the investigator/study staff immediately if they experienced a cellulitis-like reaction following vaccination on Day 1 through Day 28 and to attend an unscheduled clinic visit within 24 hours (up to 3 days if on a weekend) for evaluation. Criteria for a cellulitis-like reaction required all three of the following:

- Grade 3 injection site pain
- Grade 3 injection site erythema
- Grade 3 injection site induration

Cellulitis was defined as the presence of a cellulitis-like reaction with laboratory confirmation of leukocytosis/neutropenia and/or positive culture and sensitivities of wound aspirate in case of injection site necrosis or abscess.

Reviewer comment: The criteria for cellulitis-like reaction were similar to the criteria used to evaluate increased postmarketing reports of severe cellulitis and/or injection site swelling associated with administration of Afluria TIV in 2011. The Applicant agreed to our pre-IND request to monitor and summarize any severe cellulitis-like reactions at the injection site in this study. The Applicant now monitors all postmarketing reports of cellulitis and large/extensive injection site swelling reactions on a monthly basis and, if such reactions occur in clinical studies, subjects are recalled for evaluation. The Applicant's definitions of cellulitis-like reaction and cellulitis have been standardized as outlined in the safety monitoring procedures. Evaluation of subjects in CSLCT-QIV-13-01 who returned to clinic for assessment of a cellulitis-like reaction included a temperature measurement, CBC, and wound culture as indicated.

Subjects were instructed to contact the investigator/study staff immediately if they experienced signs or symptoms of an influenza-like illness (ILI) following vaccination on

Day 1 through Day 21 and to attend an unscheduled visit within 72 hours of symptoms for evaluation. Criteria for ILI:

- Elevated oral temperature of ≥100.4°F (≥38.0°C) (or a clear history of fever or chills), AND
- At least one flu-like symptom (including sore throat, cough, myalgia, headache, malaise, rhinitis, otitis media, nausea, and vomiting).

Antiviral medications, if indicated, were not administered until after two nasal swabs (right and left nostrils) and a throat swab were collected for influenza A/B Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

Reviewer comment: For the purposes of this study, the definition of ILI was sufficiently similar to the CDC national surveillance case definition of ILI: Temperature ≥100°F (≥37.8°C) AND cough and/or sore throat without a known cause other than influenza.

Definitions and Criteria for the Assessment of Severity and Causality of AEs
Definitions of AEs and SAEs were consistent with those in 21 CFR 312.32.

Solicited AEs and the severity grading scales for both solicited and unsolicited AEs including SAEs are presented in Table 6:

Table 6: Severity Grading Scales for Adverse Events – CSLCT-QIV-13-01

Solicited Local Reactogenicity	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Pain	None	Does not interfere with activity	Interferes with activity	Prevents daily activity
Redness/erythema	< 20 mm	≥20 mm to < 50 mm	≥50 mm to < 100 mm	≥ 100 mm
Induration/swelling	< 20 mm	≥20 mm to < 50 mm	≥50 mm to < 100 mm	≥ 100 mm
Solicited Systemic Symptoms	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
Fever	<38.0°C <100.4°F	≥38.0°C to <38.5°C ≥100.4°F to <101.3°F	≥38.5°C to <39.0°C ≥101.3°F to <102.2°F	≥39.0°C ≥102.2°F
Headache Malaise Myalgia Chills Nausea Vomiting	None	Does not interfere with activity	Interferes with activity	Prevents daily activity
Unsolicited Adverse Events	**Grade 0 (none)**	**Grade 1 (mild)**	**Grade 2 (moderate)**	**Grade 3 (severe)**
--	n/a	Easily tolerated, does not interfere with normal everyday activities	Discomfort sufficient to cause some interference with normal everyday activities	Symptoms prevent normal, everyday activities

Source: Adapted from Module 5, CSR CSLCT-QIV-13-01, Tables 9.5-2 and 9.5-3 and text, pp.56-57.

Reviewer comment: The solicited AE parameters were consistent with those in prior Seqirus influenza studies. Subjects used three diary cards to record AEs: a 7-day solicited AE diary, an unsolicited AE diary for Day 1 through Day 21, and, because these diary cards were reviewed and returned at the Day 21 clinic visit, another unsolicited AE diary card was issued on Day 21 for Days 22 through 28.

Adverse Events of Special Interest (AESIs) – The protocol included monitoring for AESIs that met the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI definition of events of "scientific and medical concern specific to the

Applicant's product or program, for which ongoing monitoring and rapid communication by the investigator to the Applicant can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study sponsor to other parties (e.g., regulators) might also be warranted". For Afluria QIV, these events included rare medically significant events selected based on prior experience with Afluria TIV and/or because they have been identified as potential AEs for the pharmacologic class of inactivated influenza vaccines. AESIs were recorded on the SAE page of the eCRF as serious or non-serious "medically significant" events, and included the following:

- Optic neuritis
- Encephalitis
- Thrombocytopenia
- Vasculitis
- Guillain-Barre syndrome
- Bell's palsy
- Transverse myelitis
- Demyelinating disorders

Reviewer comment: These events appear in the postmarketing section of the Afluria TIV PI as uncommon events that have been associated either with Afluria TIV or other influenza vaccines. They are monitored as part of the Afluria TIV PVP and are reported to OBE/DE in Periodic Safety Update Reports. Please see Section 6.1.2, Design Overview, for comments on adding large/extensive injection site swelling and cellulitis-like reactions to the PVP as AESIs.

Assessment of causality – Solicited AEs were considered vaccine-related. All other AEs were assessed by the investigator as either related or not related to the study vaccines. Factors considered in this assessment included: known pharmacology, clinical and/or pathophysiological plausibility, similarity to events previously reported following vaccination with similar products, and temporal relationship.

6.1.8 Endpoints and Criteria for Study Success

Primary Immunogenicity Endpoints

The immunogenicity of the study vaccines was evaluated by measuring HI titers to each of the four virus strains included in the vaccines at 21 days following vaccination. The non-inferiority (NI) of Afluria QIV compared to Afluria TIV-1 and Afluria TIV-2 was assessed for eight co-primary endpoints of Day 21 HI geometric mean titer (GMT) ratios and seroconversion rate (SCR) differences for each of the four vaccine virus strains for the immunogenicity population comprised of both age groups:

- GMT ratio for the A/H1N1 strain
- GMT ratio for the A/H3N2 strain
- GMT ratio for the B strain (Yamagata lineage)
- GMT ratio for the B strain (Victoria lineage)
- SCR difference for the A/H1N1 strain
- SCR difference for the A/H3N2 strain
- SCR difference for the B strain (Yamagata lineage)
- SCR difference for the B strain (Victoria lineage)

The GMT ratio was defined as: GMT Afluria TIV / GMT Afluria QIV.

- Success criteria for non-inferiority (NI margin): GMT ratio of Afluria TIV / Afluria QIV should not exceed 1.5.

The SCR difference was defined as: SCR Afluria TIV – SCR Afluria QIV.

- SCR was defined as the percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a ≥4-fold rise in post-vaccination HI titer.
- Success criteria for NI margin: The SCR difference SCR Afluria TIV – SCR Afluria QIV should not exceed 10%.

Secondary Immunogenicity Endpoints

- The NI of Afluria QIV compared to Afluria TIV-1 and Afluria TIV-2 was assessed separately within each age group (18 through 64 years and ≥ 65 years) by the co-primary endpoints of HI GMT and SCR for each virus strain included in the vaccines as described for the primary endpoint.

Reviewer comment: The study was powered to test a NI hypothesis for each of the two age cohorts.

- Immunological superiority of the alternate B strain (i.e., the influenza B strain included in the QIV but not in the TIV formulation) in Afluria QIV was assessed in each of the two age groups (18 through 64 years and ≥65 years) and overall by the co-primary endpoints of HI GMT and SCR for each B strain. Immunological superiority of the alternate B strain was defined as a lower bound (LB) of the 95% CI for the GMT ratio of Afluria QIV / Afluria TIV > 1.0 and a LB of the 95% CI for the SCR difference Afluria QIV – Afluria TIV > 0.
- The immunogenicity of Afluria QIV, Afluria TIV-1, and Afluria TIV-2 was also assessed in terms of HI antibodies for each of the four vaccine virus strains. Serum HI antibodies were used to calculate:
    - GMT: geometric mean of HI titers pre-vaccination (Day 1) and post-vaccination (Day 21);
    - The percentage of subjects with an HI titer ≥1:40 (HI ≥1:40) at Day 1 and Day 21;
    - SCR: percentage of subjects with either a pre-vaccination HI titer <1:10 and a post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a ≥4-fold rise in post-vaccination HI titer
    - Geometric mean fold increase (GMFI) in GMT from Day 1 to Day 21 where GMFI was defined as the geometric mean of the fold increases of the post-vaccination HI titer over the pre-vaccination HI titer.

Reviewer comment: The primary and secondary immunogenicity endpoints were appropriate. See previous reviewer comment regarding study design in Section 6.1.2.

Secondary Safety Endpoints

- Solicited local and systemic AEs for 7 days post-vaccination (Day 1 to Day 7)
- Cellulitis-like reaction, cellulitis, and Grade 3 induration/swelling at the injection site for 28 days following vaccination
- Unsolicited AEs for 28 days following vaccination
- SAEs for 6 months following vaccination

6.1.9 Statistical Considerations & Statistical Analysis Plan

Please see the statistical review for a complete discussion of the statistical analysis plan.

The primary objective of CSLCT-QIV-13-01 was to demonstrate that vaccination with Afluria QIV elicits a non-inferior immune response as compared to Afluria TIV-1 and Afluria TIV-2 among adults aged ≥18 years. In mathematical notation, the statistical hypotheses to be tested for the primary immunogenicity analysis corresponded to:

- H0: Ri > 1.5, for any strain
- Ha: Ri ≤ 1.5, for any strain

and

- H0: Di > 10, for any strain
- Ha: Di ≤ 10, for any strain

where Ri was any of the four strain-specific Day 21 post-vaccination GMT ratios:

- (Afluria TIV-1) / (Afluria QIV) for B/Yamagata strain
- (Afluria TIV-2) / (Afluria QIV) for B/Victoria strain
- (Afluria TIV-1+ Afluria TIV-2) / (Afluria QIV) for A/H1N1 strain
- (Afluria TIV-1+ Afluria TIV-2) / (Afluria QIV) for A/H3N2 strain

and Di is the four strain-specific Day 21 post-vaccination SCR difference:

- (Afluria TIV-1) - (Afluria QIV) for B/Yamagata strain
- (Afluria TIV-2) - (Afluria QIV) for B/Victoria strain
- (Afluria TIV-1+ Afluria TIV-2) - (Afluria QIV) for A/H1N1 strain
- (Afluria TIV-1+ Afluria TIV-2) - (Afluria QIV) for A/H3N2 strain.

Because the A/H1N1 and A/H3N2 virus strains were common to both TIV comparators, data for each of these strains from the two TIV groups were pooled for comparison to the QIV vaccine.

No adjustment was made for multiple comparisons because the sample size and power were calculated based on eight co-primary endpoints. This was acceptable to the statistical reviewer.

For the primary immunogenicity analyses, the GMT ratio was adjusted for the following covariates: treatment group, age sub-group (18-49, 50-64, 65-74, and ≥ 75 years), sex, influenza vaccination in the prior year, pre-vaccination GMT, and investigator site. Secondary analyses of the primary endpoint were also performed with adjustment for individual covariates to evaluate the contribution of these factors to variation in the immune response.

For safety endpoints, descriptive statistics were used to summarize the number and percentage of subjects experiencing at least one event by treatment group overall and by age cohort. The number of events was also presented.

<u>Sample Size</u>

The sample size was calculated to provide 80% power to demonstrate non-inferiority in each age stratum (and consequently was powered overall) for SCRs and GMTs for each of the 4 vaccine virus strains (total of 8 co-primary endpoints) using a one-sided alpha of 0.025 for each comparison. No adjustment was made for multiple endpoints. NI margins of 10% and 1.5 were employed for the SCR difference and GMT ratio, respectively. Assumptions included a SCRs of 50% for all strains with no difference between Afluria TIV and QIV, and GMT ratios of 1.0, again no difference between Afluria TIV and QIV.

Under these assumptions, an evaluable sample size of n=826 for Afluria QIV and n=413 for Afluria TIV per age stratum (total n=1652 per age stratum and total n=3304 overall) was calculated as providing 98.2% power to detect differences in SCR for each A strain and 91.3% power for each B strain, providing overall 80.38% power for the four SCR tests. For GMT ratio tests, each A strain had 100% power and each B strain had 99.8% power, providing 99.6% power for the four GMT ratio tests and, consequently, 80.06% power for the eight co-primary endpoints in each age stratum. Allowing for a 5% dropout rate, a total enrollment of 3480 subjects was planned.

The calculated sample size also provided 80% power to detect the superiority of Afluria QIV against the alternate B strain in each of the two Afluria TIV vaccines for the SCR difference and GMT ratio, assuming that the SCR difference was at least 10% (i.e., SCR of 40% for TIV and 50% for QIV) and the GMT ratio was at least 1.3. No adjustment for multiplicity was made for testing the superiority of the two Afluria QIV B strains against the alternate TIV B strain.

Protocol Deviations and Violations

Protocol deviations listings were reviewed by Seqirus prior to finalization of the population datasets and prior to unblinding. The list was used to determine which subjects should be excluded from the Evaluable or Per Protocol populations [see CSR Appendix 16.1.9, SAP, Analysis Set Specification Document, Section]. The following major violations excluded a subject from the Evaluable Population:

- Pre- and/or post-vaccination blood samples not provided
- Laboratory-confirmed influenza infection

Missing Data

Missing data were not imputed. HI titers <1:10 were assigned a value of 1:5 for the purpose of GMT calculations.

Interim Analysis

An interim analysis of immunogenicity and safety data collected from the active study period (Day 1 to Day 28) was performed.

Changes in the Conduct of the Study or Planned Analyses

- An interim analysis and CSR were added to include immunogenicity and safety data collected from Day 1 to Day 28. The final CSR would integrate the interim data and safety data collected through the final six month follow-up contact.
- The protocol was amended to align with the ICF and allow for an optional off-study additional vaccination with licensed Afluria TIV after Day 28 for subjects who were at increased risk of serious complications of influenza.

Reviewer comment: Review of concomitant medication listings and the electronic datasets revealed that five subjects (three CSL QIV, one CSL TIV-1, and one CSL TIV-2) received a prophylactic seasonal influenza vaccine during the post-study vaccination period. Review of safety data for these subjects suggested that receipt of off study influenza vaccination had no significant impact on interpretation of the study results.

- Immunogenicty and safety analyses were conducted according to sex, racial, and ethnicity subgroups.

- For solicited AEs, each parameter had its own denominator. Subjects were excluded from the denominator for an AE only if the severity grade was missing or unknown for all 7 days of follow-up. In such cases, another category for missing values was added as a row or column to summary tables to indicate the number of subjects for whom the variable was recorded as a missing value. If , for a given parameter, the severity grade was missing for only some of the days, then the severity was imputed as the maximum of the previous and next non-missing value in order to calculate the aggregate 7-day severity grade.
- For tables summarizing all solicited and unsolicited AEs, a summary of the severity for AEs Grade ≥ 1 was added.
- A listing of severe AEs was created.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Analysis populations were defined as follows:

- Full Analysis Set (FAS): The FAS comprised all subjects who gave informed consent and who were randomized to treatment. Screening failures were not included in the FAS but were summarized in disposition tables and listed. The FAS was used to summarize subject baseline characteristics.
- Safety Population (SP): The SP included all randomized subjects (FAS) who received at least one dose of study vaccine and provided any safety follow-up data. The SP was used to summarize all safety data.
- Evaluable Population (EP): The EP included all randomized subjects in the FAS who:
    - were vaccinated with study vaccine at Visit 1 (Day 1);
    - provided both pre- and post-vaccination serologies at Visit 1 and Visit 2 (Exit Visit, ~Day 21);
    - did not experience a laboratory-confirmed influenza illness between Visit 1 and Visit 2 (Days 1 and ~21); and
    - did not receive a contraindicated medication during the study that was assessed as potentially impacting immunogenicity results.
- Per Protocol Population (PPP): The PPP was used for the primary and secondary immunogenicity analyses and included subjects in the Evaluable Population minus any subjects with protocol deviations assessed as potentially affecting immunogenicity results. Subjects included in the PPP were determined prior to unblinding. Duplicate analyses were planned based on the EP in the event that there was a > 1% difference in the total number of subjects in either of the two age strata (18-64 and ≥65 years) between the PPP and EP.

6.1.10.1.1 Demographics

There were no large differences in the distribution of demographic or baseline characteristics among the three treatment groups in the FAS population. Overall, there were more female (57.2%) than male (42.8%) subjects (U.S. population 51% and 49%, respectively). The majority of subjects were white (82.3%) and non-Hispanic/Latino (94.9%) (U.S. population 77% and 83%, respectively). Black/African American and Hispanic/Latino subjects comprised 15.8% and 4.9% of the FAS, respectively (U.S. population 13% and 17%, respectively). Other racial groups comprised <2% of the population. Baseline characteristics were similar between age cohorts with the

exception of a higher proportion of black/African American subjects in the 18-64 years age cohort (25.5%) as compared to the ≥65 years cohort (6.0%).

The mean age of all subjects was 58.3 years (SD 18.04); 43.5 years (SD13.48) for the 18-64 years age cohort; and 73.1 years (SD 5.59) for the ≥ 65 years age cohort. The proportions of subjects in the subgroups (FAS) were as follows: 18-49 years 29.3%; 50-64 years (20.7%); 65-74 years (31.1%); and ≥75 years (19.0%).

Reviewer comment: Differences in demographic and baseline characteristics were generally small among the treatment groups and not likely to have had a significant impact on the interpretation of study results. Relative to the U.S. population, females and whites were somewhat overrepresented, and Hispanics/Latinos were significantly underrepresented. Relative to the total US population, blacks and African Americans were overrepresented in the younger age cohort but underrepresented in the ≥65 years age cohort. Asians were also underrepresented (5.4% of the U.S. population, <1% of the study population). The proportions of subjects in each age sub-group were within the pre-specified protocol targets (for 18-64 years, a maximum of 60% in either sub-strata, and for ≥65 years, a minimum of 30% in the ≥75 years sub-stratum).[53]

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Influenza Vaccination History

Of the 3484 subjects in the FAS, 3039 (87.2%) reported ever having received an influenza vaccine including 63.3% vaccinated in the 12 months prior to enrollment. A higher percentage of subjects ≥65 years of age reported influenza vaccination in the prior 12 months as compared to adults 18-64 years of age (81.6% vs 45.0%).

Medical History

The most common pre-existing conditions among all subjects in the FAS, categorized by MedDRA system organ class (SOC), were surgical and medical procedures (54.2%), vascular disorders (42.8%), and metabolism and nutrition disorders (40.6%). Similar proportions of conditions were reported across treatment groups and between age cohorts, although a higher proportion of adults ≥65 years reported any prior medical history as compared to adults 18-64 years of age (98.8% vs 81.9%). A total of 394 (11.3%) subjects reported a previous history of benign or malignant cysts or neoplasms. A total of 1040 (29.9%) subjects reported immune system disorders, all of which were allergies or hypersensitivity disorders. No immunodeficiency disorders were reported. A total of 469 (13.4%) of subjects reported type 1 or type 2 diabetes mellitus. A total of 109 (3.1%) of subjects reported obesity (weight but not height was measured, and BMI was not calculated in the study).

Concomitant Medications

A total of 94.7% of subjects ≥65 years and 68.7% of adults 18-64 years of age (81.7% overall) were taking medications at the time of vaccination.

Reviewer comment: Medical history and concomitant medication use were reflective of an adult and older adult population. Evaluation of the electronic datasets for potentially immunosuppressive agents indicated that approximately 233 subjects were taking some form of steroid during the study. The vast majority were topical or inhaled steroids for allergic or dermatologic conditions or asthma or chronic obstructive pulmonary disease (COPD), and were allowed by the

protocol. A few subjects received intra-articular steroids for arthritis or low dose/short course oral steroids for acute respiratory or musculoskeletal conditions (treatment of AEs). One subject was taking hydroxycarbamide for polycythemia vera/thrombocytosis. Another began oral methotrexate on Day 113 for granulomatosis with polyangiitis (described in Section 6.1.12.5). No large imbalances were found across treatment groups. Overall, concomitant medications should not have significantly affected the interpretation of immunogenicity or safety results.

A total of 1060 subjects in the FAS received HMG CoA reductase inhibitors (statins) for hypercholesterolemia during the study. The vast majority were on chronic therapy beginning months to years prior to enrollment. Because statins are known to have immunomodulating effects, a recent observational study explored the effect of chronic statin use on the immunogenicity of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine in adults ≥65 years of age in four countries including the U.S., and found lower immune responses to influenza antigens in patients receiving statins.[1,5] A second retrospective cohort study evaluated the association of chronic statin use on the effectiveness of influenza vaccination against medically attended acute respiratory illness (MAARI) in patients belonging to a large managed care organization in the U.S. over nine influenza seasons.[44] Lower influenza vaccine effectiveness against MAARI was observed in patients receiving statins. This association requires further evaluation for influenza vaccines in general. CSLCT-QIV-13-01 was not designed to evaluate the effect of statin use on immunogenicity. Evaluation of the electronic datasets indicated that the proportions of subjects receiving statins were balanced across treatment groups (approximately 30% of subjects in each group).

6.1.10.1.3 Subject Disposition

Table 7 presents the disposition of subjects and analysis populations.

Table 7: Subject Disposition and Analysis Populations, All Subjects ≥18 Years (Full Analysis Set) – CSLCT-QIV-13-01

Population	QIV n=1741	TIV-1 n=871	TIV-2 n=872	Total N=3834
Screened, n	--	--	--	3673
Screening failures, n	--	--	--	185
Withdrew prior to randomization, n	--	--	--	4
Full Analysis Set, n(%)	1741	871	872	3484
Randomized in error, not vaccinated, n	--	--	--	4
Vaccinated but provided no safety data, n	--	--	--	31
Safety Population, n(%)	1721 (98.9)	864 (99.2)	864 (99.1)	3449 (99.0)
Excluded from FAS, n	--	--	--	35
Evaluable Population, n(%)	1704 (97.9)	857 (98.4)	854 (97.9)	3415 (98.0)
Excluded from FAS due to incomplete serologies and/or receipt of prohibited medications, n	--	--	--	69
Per Protocol Population, n(%)	1691 (97.1)	854 (98.0)	850 (97.5)	3395 (97.4)
Excluded from EP due to protocol deviations*, n	--	--	--	20
Completed study, n(%)	1686 (96.8)	852 (97.8)	850 (97.5)	3388 (97.2)
Discontinued from study, n(%)	55 (3.2)	19 (2.2)	22 (2.5)	96 (2.8)
Adverse event, n	0	0	0	0
Protocol violation, n	0	0	0	0
Lost to follow-up, n(%)	46 (2.6)	18 (2.1)	18 (2.1)	82 (2.4)
Withdrawal by subject, n	2	0	2	4

Population	QIV n=1741	TIV-1 n=871	TIV-2 n=872	Total N=3834
Physician decision, n	0	0	0	0
Death, n(%)	5 (0.3)	0	1 (0.1)	6 (0.2)
Other (randomized in error, not vaccinated), n(%)	2	1	1	4

Source: Adapted from Module 5, CSLCT-QIV-13-01, CSR Tables 11.1-1, 14.1.1.1, and text pp.78-85.
*Twenty subjects in the EP had 21 protocol deviations that excluded them from the PPP: outside Day 21 window (n=11); alcohol abuse (n=1); enrolled in another trial in previous 30 days (n=1); randomization to incorrect age stratum (n=6); vaccine storage temperature deviation discovered after vaccination (n=2).

Reviewer comment: Overall, 2.8% of subjects discontinued the study, most were lost to follow-up (2.4%), and none were due to AEs. The dropout/discontinuation rates were low, similar across treatment groups, and should not have introduced significant bias or influenced the interpretation of immunogenicity or safety results.

Subject disposition for the two age cohorts was similar to the overall study population. Table 8 presents the SP and PPP (also presented in the PI) by age cohort.

Table 8: Safety and Per Protocol Populations by Age Cohort – CSLCT-QIV-13-01

Age Cohort	Population	Afluria QIV n(%)	TIV-1 (YAM) n(%)	TIV-2 (VIC) n(%)	Total N(%)
18-64 years	Safety Population	854 (98.0)	428 (98.6)	430 (98.6)	1712 (98.3)
18-64 years	Per Protocol Population	835 (95.9)	424 (97.7)	421 (96.6)	1680 (96.5)
≥65 years	Safety Population	867 (99.7)	436 (99.8)	434 (99.5)	1737 (99.7)
≥65 years	Per Protocol Population	856 (98.4)	430 (98.4)	429 (98.4)	1715 (98.4)

Source: Adapted from Module 5, CSLCT-QIV-13-01, CSR Tables 14.1.1.1 and 14.1.1.2.
Abbreviations: TIV-1(YAM)= 2014-2015 US licensed Afluria TIV containing B/Yamagata lineage; TIV-2(VIC)=Afluria TIV containing the alternate B strain (B/Victoria lineage).
Percentages based on FAS in each age group.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The immunogenicity of each study vaccine was assessed 21 days after vaccination by measuring HI antibody titers to the four virus strains included in the vaccines. The NI of Afluria QIV compared to Afluria TIV-1 and TIV-2 was assessed for the co-primary endpoints of HI GMT ratios and SCR differences for each of the four virus strains as described in Section 6.1.8, Endpoints and Criteria for Success.

Table 9 presents results of post-vaccination HI GMTs, SCRs, and analyses of NI for adjusted GMT ratios and SCR differences for each vaccine virus strain in adults ≥18 years of age (Per Protocol Population).

Reviewer comment: Table 9 presents a revised primary analysis provided by the Applicant (STN 125254.565.12) in response to a statistical reviewer request to follow models specified in the SAP to: 1) exclude a non-significant age-by-vaccine interaction term in the NI post-vaccination GMT analysis; and 2) present SCR differences with exact 95% CIs. Please see the statistical review for further discussion.

Table 9: Analyses of Non-inferiority, GMT ratios and SCR differences, of Afluria QIV Relative to Afluria TIV 21 Days Post-Vaccination in Adults ≥18 Years (Per Protocol Population)

Strain	QIV GMT[1] (n=1691)	Pooled TIV or TIV-1 or TIV-2 GMT (n=1704)[2]	GMT ratio (95%CI)[3]	QIV SCR[4] (n=1691)	Pooled TIV or TIV-1 or TIV-2 SCR (n=1704)[2]	SCR Difference (95%CI)[5]	Met both NI criteria?[6]
A/H1N1	302.1	281.1	0.93 (0.88,0.99)	38.8	37.7	-1.1 (-4.5,2.3)	Yes
A/H3N2	488.5	454.5	0.93 (0.88,0.98)	40.9	39.3	-1.7 (-5.0,1.7)	Yes
B/YAM	64.1	56.0	0.87 (0.82,0.93)	31.0	27.8	-3.2 (-7.4,0.9)	Yes
B/VIC	87.6	83.0	0.95 (0.88,1.03)	40.3	38.7	-1.6 (-5.8,2.5)	Yes

Source: STN 125254/565.12, Module 5, CSLCT-13-01 CSR, Tables 11.4-1, 14.2.1.1, and 14.2.2.1.1
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; AH3N2=A/Texas/50/2012 (H3N2)-like virus; B/YAM=B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC=B/Brisbane/60/2008-like virus (B/Victoria lineage); QIV=Afluria QIV; TIV-1=Afluria TIV-1 containing B/Yamagata; TIV-2=Afluria TIV-2 containing B/Victoria; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval, NI=non-inferiority.
[1]GMTs adjusted for covariates: treatment group, age subgroup, sex, vaccination history, pre-vaccination GMT, and investigator site.
[2]TIV-1 and TIV-2 are pooled for the A strain analyses, (n=1704). TIV-1 (B/Yamagata), n=854. TIV-2 (B/Victoria), n=850.
[3]GMT ratio=Afluria TIV over Afluria QIV. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[4]SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
[5]SCR difference=Afluria TIV SCR minus Afluria QIV SCR. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[6]Non-inferiority criteria for GMT ratio: upper bound (UB) of the two-sided 95% CI on the ratio of pooled TIV or TIV-1 or TIV-2 / Afluria QIV should not exceed 1.5. NI criteria for SCR difference: UB of the two-sided 95% CI on the difference between SCR pooled TIV or TIV-1 or TIV-2 – Afluria QIV should not exceed 10%.

Reviewer comment: Afluria QIV met the eight pre-specified co-primary endpoints required to demonstrate NI to the Afluria comparator TIV vaccines in adults ≥18 years of age. As specified in the SAP, the primary NI analyses were not conducted in the EP because there was less than 1% variation between the EP and PPP in the two age cohorts (18-64 and ≥65 years). GMT ratios calculated from unadjusted GMTs were only slightly higher than GMT ratios adjusted for covariates (see CSLCT-QIV-13-01 CSR Table 14.2.1.1) and also met NI criteria.

6.1.11.2 Analyses of Secondary Endpoints

Non-inferiority of Afluria QIV by Age Cohort

The NI of Afluria QIV compared to Afluria TIV-1 and TIV-2 was assessed separately within each age cohort (18-64 years and ≥65 years) by the co-primary endpoints of HI GMT and SCR for each virus strain included in the vaccines as described for the primary endpoint. SCR differences were presented with exact 95% CIs in accordance with the SAP (and in response to the statistical reviewer's request, STN 125254/565.12).

Table 10 presents results of post-vaccination HI GMTs, SCRs, and analyses of NI for adjusted GMT ratios and SCR differences for each vaccine virus strain in adults 18 through 64 years of age (Per Protocol Population).

Table 10: Analyses of Non-inferiority, GMT ratios and SCR differences, of Afluria QIV Relative to Afluria TIV 21 Days Post-vaccination in Adults Aged 18 through 64 Years (Per Protocol Population) – CSLCT-QIV-13-01

Strain	QIV GMT[1] (n=835)	Pooled TIV or TIV-1 or TIV-2 GMT (n)[2]	GMT ratio (95%CI)[3]	QIV SCR[4] (n=835)	Pooled TIV or TIV-1 or TIV-2 SCR (n)[2]	SCR Difference (95%CI)[5]	Met both NI criteria?[6]
A/H1N1	432.7	402.8	0.93 (0.85,1.02)	51.3	49.1	-2.1 (-6.9,2.7)	Yes
A/H3N2	569.1	515.1	0.91 (0.83,0.99)	56.3	51.7	-4.6 (-9.4,0.2)	Yes
B/YAM	92.3	79.3	0.86 (0.76,0.97)	45.7	41.3	-4.5 (-10.3,1.4)	Yes
B/VIC	110.7	95.2	0.86 (0.76,0.98)	57.6	53.0	-4.6 (-10.5,1.2)	Yes

Source: STN 125254/565, Module 5, CSLCT-13-01 CSR, Tables 11.4-2, 14.2.4.1, and STN 125254/565.12, Module 5, CSLCT-13-01 CSR Table 14.2.4.2.1
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; AH3N2=A/Texas/50/2012 (H3N2)-like virus; B/YAM=B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC=B/Brisbane/60/2008-like virus (B/Victoria lineage); QIV=Afluria QIV; TIV-1=Afluria TIV-1 containing B/Yamagata; TIV-2=Afluria TIV-2 containing B/Victoria; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval, NI=non-inferiority.
[1]GMTs adjusted for covariates: treatment group, sex, vaccination history, pre-vaccination GMT, and investigator site.
[2]TIV-1 and TIV-2 are pooled for the A strain analyses, (n=845). TIV-1 (B/Yamagata), n=424. TIV-2 (B/Victoria), n=421.
[3]GMT ratio=Afluria TIV over Afluria QIV. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[4]SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
[5]SCR difference=Afluria TIV SCR minus Afluria QIV SCR. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[6]Non-inferiority criteria for GMT ratio: upper bound (UB) of the two-sided 95% CI on the ratio of pooled TIV or TIV-1 or TIV-2 / Afluria QIV should not exceed 1.5. NI criteria for SCR difference: UB of the two-sided 95% CI on the difference between SCR pooled TIV or TIV-1 or TIV-2 – Afluria QIV should not exceed 10%.

Reviewer comment: Afluria QIV met the eight pre-specified co-secondary endpoints required to demonstrate NI to the Afluria comparator TIV vaccines in adults 18 through 64 years of age. GMT ratios calculated from unadjusted GMTs were only slightly higher than GMT ratios adjusted for covariates (see CSLCT-QIV-13-01 CSR Table 14.2.4.1) and also met NI criteria.

Table 11 presents results of post-vaccination HI GMTs, SCRs, and analyses of NI for adjusted GMT ratios and SCR differences for each vaccine virus strain in adults ≥65 years of age (Per Protocol Population).

Table 11: Analyses of Non-inferiority, GMT ratios and SCR differences, of Afluria QIV Relative to Afluria TIV 21 Days Post-Vaccination in Adults ≥65 Years (Per Protocol Population) – CSLCT-QIV-13-01

Strain	QIV GMT[1] (n=856)	Pooled TIV or TIV-1 or TIV-2 GMT (n)[2]	GMT ratio (95%CI)[3]	QIV SCR[4] (n=856)	Pooled TIV or TIV-1 or TIV-2 SCR (n)[2]	SCR Difference (95%CI)[5]	Met both NI criteria?[6]
A/H1N1	211.4	199.8	0.95 (0.88,1.02)	26.6	26.4	-0.2 (-5.0,4.5)	Yes
A/H3N2	419.5	400.0	0.95 (0.89,1.02)	25.9	27.0	1.1 (-3.7,5.8)	Yes
B/YAM	43.3	39.1	0.90 (0.84,0.97)	16.6	14.4	-2.2 (-8.0,3.6)	Yes
B/VIC	66.1	68.4	1.03 (0.94,1.14)	23.5	24.7	1.2 (-4.6,7.0)	Yes

Source: STN 125254/565, Module 5, CSLCT-13-01 CSR, Tables 11.4-3, 14.2.4.1, and STN 125254/565.12, Table 14.2.4.2.1
Abbreviations: A/H1N1=A/California/7/2009 (H1N1) pdm09-like virus; AH3N2=A/Texas/50/2012 (H3N2)-like virus; B/YAM=B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC=B/Brisbane/60/2008-like virus (B/Victoria lineage); QIV=Afluria QIV; TIV-1=Afluria TIV-1 containing B/Yamagata; TIV-2=Afluria TIV-2 containing B/Victoria; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval, NI=non-inferiority.
[1]GMTs adjusted for covariates: treatment group, sex, vaccination history, pre-vaccination GMT, and investigator site.
[2]TIV-1 and TIV-2 are pooled for the A strain analyses, (n=859). TIV-1 (B/Yamagata), n=430. TIV-2 (B/Victoria), n=429.
[3]GMT ratio=Afluria TIV over Afluria QIV. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[4]SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
[5]SCR difference=Afluria TIV SCR minus Afluria QIV SCR. Afluria TIV-1 and TIV-2 are pooled for the A strains.
[6]Non-inferiority criteria for GMT ratio: upper bound (UB) of the two-sided 95% CI on the ratio of pooled TIV or TIV-1 or TIV-2 / Afluria QIV should not exceed 1.5. NI criteria for SCR difference: UB of the two-sided 95% CI on the difference between SCR pooled TIV or TIV-1 or TIV-2 – Afluria QIV should not exceed 10%.

Reviewer comment: Afluria QIV met the eight pre-specified co-secondary endpoints required to demonstrate NI to the Afluria comparator TIV vaccines in adults ≥65 years of age. GMT ratios calculated from unadjusted GMTs were only slightly higher than GMT ratios adjusted for covariates (see CSLCT-QIV-13-01 CSR Table 14.2.4.1) and also met NI criteria. As compared to adults 18-64 years of age, adults ≥65 years of age had lower post-vaccination GMTs and SCRs, particularly for the B strains and A/H1N1. Lower immune responses to influenza antigens in older adults have been observed in the past, especially to the B strains. This may reflect immunosenesence or, in the case of persons previously vaccinated with high baseline titers, difficulty achieving a 4-fold rise in titers.

Immunological Superiority of the Alternate B Strain by GMT Ratio and SCR

The immunological superiority of Afluria QIV versus the alternate B strain (i.e., the B strain not included in the comparator TIV) was assessed separately within each age cohort (18-64 years and ≥65 years) and overall) by GMT ratios and SCR differences (see Section 6.1.8). Table 12 presents the results of these analyses which showed that Afluria QIV met superiority success criteria for both GMT ratios and SCR differences for both B strains included in the vaccine, overall and for each age group.

Table 12: Post-Vaccination HI GMTs, SCRs, and Analyses of Superiority of Afluria QIV Relative to Afluria TIV for the Alternate B Strain in Adults ≥18 Years of Age and by Age Cohort (Per Protocol Population) – CSLCT-QIV-13-01

Strain	QIV GMT[1]	TIV-1 (B/YAM) or TIV-2 (B/VIC) GMT (n)[2]	GMT ratio (95%CI)[3]	QIV SCR[4]	TIV-1 (B/YAM) or TIV-2 (B/VIC) SCR (n)[2]	SCR Difference (95%CI)[5]	Met both NI criteria?[6]
≥18 yrs (overall)	**N=1691**	**--**	**--**	**N=1691**	**--**	**--**	**--**
B/YAM	62.9	42.7[7]	1.47[13] (1.38,1.57)	31.0	15.6[7]	15.3[15] (11.2,19.4)	Yes
B/VIC	86.9	55.4[8]	1.57[14] (1.45,1.70)	40.3	20.3[8]	20.1[16] (16.0,24.1)	Yes
18-64 yrs	**n=835**	**--**	**--**	**n=835**	**--**	**--**	**--**

B/YAM	89.9	53.8[9]	1.67[13] (1.50,1.87)	45.7	22.8[9]	22.9[15] (17.1,28.6)	Yes
B/VIC	113.5	64.3[10]	1.76[14] (1.55,2.01)	57.6	29.0[10]	28.6[16] (22.9,34.2)	Yes
≥65 yrs	**n=856**	**--**	**--**	**n=856**	**--**	**--**	**--**
B/YAM	43.8	33.6[11]	1.30[13] (1.21,1.40)	16.6	8.6[11]	8.0[15] (2.2,13.8)	Yes
B/VIC	64.1	46.3[12]	1.38[14] (1.27,1.51)	23.5	11.6[12]	11.9[16] (6.0,17.6)	Yes

Source: STN 125254/565, Module 5, CSLCT-QIV-13-01 CSR, Tables 11.4-4, 14.2.4.3, and 14.2.4.4; STN 125254/565.1, response to 15Dec2015 request for information regarding errors to Table 11.4-4, footnotes l, m, n, and o. STN 125254/565.12, Module 5, CSLCT-QIV-13-01 CSR, Table 14.2.4.4.1,
Abbreviations: B/YAM=B/Massachusetts/2/2012-like virus (B/Yamagata lineage); B/VIC=B/Brisbane/60/2008-like virus (B/Victoria lineage); QIV=Afluria QIV; TIV-1=Afluria TIV-1 containing B/Yamagata; TIV-2=Afluria TIV-2 containing B/Victoria; GMT=geometric mean titer; SCR=seroconversion rate; CI=confidence interval.
Bold type indicates age cohort.
[1]GMTs adjusted for covariates: treatment group, age subgroup (for ≥18 yrs overall analyses only), sex, vaccination history, pre-vaccination GMT, and investigator site.
[2]TIV-1 (B/Yamagata), TIV-2 (B/Victoria).
[3]GMT ratio=Afluria QIV over Afluria TIV.
[4]SCR defined as percentage of subjects with either a pre-vaccination HI titer <1:10 and post-vaccination HI titer ≥1:40, or a pre-vaccination HI titer ≥1:10 and a 4-fold increase in post-vaccination HI titer.
[5]SCR difference=Afluria QIV SCR minus Afluria TIV SCR.
[6]Immunological superiority of the alternate B strain (i.e., the B strain included in Afluria QIV but not the TIV vaccine) in Afluria QIV was demonstrated if the lower bound (LB) on the two-sided 95% CI for the GMT ratio was greater than 1 and the LB on the two-sided 95% CI for the SCR difference was greater than 0.
[7]B/Yamagata serology for TIV-2 (B/Victoria), Adults ≥18 years, n=850. [i.e., HI titers against B/Yamagata were measured in subjects who received TIV-2 (B/Victoria).]
[8]B/Victoria serology for TIV-1 (B/Yamagata), Adults ≥18 years, n=854. [i.e., HI titers against B/Victoria were measured in subjects who received TIV-1 (B/Yamagata)]
[9]B/Yamagata serology for TIV-2 (B/Victoria), Adults 18-64 years, n=421.
[10]B/Victoria serology for TIV-1 (B/Yamagata), Adults 18-64 years, n=424.
[11]B/Yamagata serology for TIV-2 (B/Victoria), Adults ≥65 years, n=429.
[12]B/Victoria serology for TIV-1 (B/Yamagata), Adults ≥65 years, n=430.
[13]Ratio of Afluria QIV / TIV-2 [where HI GMTs against B/Yamagata were measured in subjects vaccinated with TIV-2(B/Victoria)]
[14]Ratio of Afluria QIV / TIV-1 [where HI GMTs against B/Victoria were measured in subjects vaccinated with TIV-1(B/Yamagata)]
[15]SCR Afluria QIV minus SCR TIV-2 [where the SCR to B/Yamagata was calculated for subjects vaccinated with TIV-2 B/Victoria.]
[16]SCR Afluria QIV minus SCR TIV-1 [where SCR to B/Victoria was calculated for subjects vaccinated with TIV-1 B/Yamagata.]

Reviewer comment: Afluria QIV met success criteria for superiority against the alternate B strain in the respective Afluria TIV-1 and TIV-2 vaccines, overall and within each age cohort (18-64 years and ≥65 years).

Reviewer comment: The Applicant's CSR contained errors in footnotes l through o to Table 11.4-4 which describes calculations used to determine superiority. The correct formulas were clarified in a response to CBERs request for information (STN 125254.565.1) and appear in Table 12.

Other Secondary Endpoints

Other secondary endpoint analyses included the calculation of pre- and post-vaccination GMTs, the percentage of subjects with post-vaccination HI titers ≥1:40, and SCRs. Some of these data have been already presented in the tabular summaries of the primary and secondary analyses of non-inferiority of this review (point estimates for

GMTs and SCRs for Afluria QIV and pooled GMTs and SCRs for TIV-1 and TIV-2, Tables 9, 10 and 11), and will only be summarized briefly in this section. Detailed results of these endpoints may be found in Tables 11.4-5, 11.4-6, 14.2.5.2, 14.2.6.2, and 14.2.7.2 of the Applicant's CSR for CSLCT-QIV-13-01 (STN 125254.565 Module 5).

- Pre-vaccination (Day 1) GMTs to each of the four vaccine virus strains were similar across treatment groups within each of the two age cohorts (18-64 years and ≥65 years). Post-vaccination (Day 21) GMTs for each A strain were similar across treatment groups within each age cohort. For each of the Afluria TIV vaccines, post-vaccination GMTs for the B strains were lower for the non-included B strain compared to the results for the Afluria QIV and the other TIV (B strain included). Similar patterns of response were observed between the two age cohorts, however, post-vaccination GMTs were lower in adults ≥65 years as compared to adults 18-64 years of age.

Reviewer comment: Lower immune responses in the elderly may be attributable to immunosenescence.

- An HI titer of ≥1:40 represents a potential surrogate marker of protection that is likely to predict clinical benefit. The pre-vaccination percentages of subjects with HI titers of ≥1:40 (% HI ≥1:40) were similar across treatment groups and between age cohorts. Post-vaccination % HI ≥1:40 for the A/strains were similar across treatment groups within each age cohort and between age cohorts while immune responses to the B strains were notably lower in adults ≥65 years of age. In recipients of Afluria QIV, the LBs on the two-sided 95% CI for the percentages of subjects with a post-vaccination HI titer ≥1:40 for A/H1N1, A/H3N2, B/Yamagata, and B/Victoria in adults 18-64 years of age were high (98.1%, 98.1%, 81.7%, and 84.2%, respectively). The LBs on the two-sided 95% CI for the % HI ≥1:40 in adults ≥65 years who received Afluria QIV were also high for the A strains but lower for the B strains (92.9%, 99.2%, 54.1%, and 65.1%, respectively).

Reviewer comment: Post-vaccination % HI ≥1:40 for the B strains in the elderly cohort were notably lower as compared to B strain responses in the younger age cohort and to A strains responses in both age cohorts. However, the pattern of lower responses to the B strain, particularly in the elderly, has been observed in previous immunogenicity studies of Afluria TIV and other inactivated influenza vaccines.

- Seroconversion rates to the A strains and the B strain(s) included in the vaccines were also similar between Afluria QIV and the TIV comparators within each age cohort. However, SCRs to all vaccine virus strains were significantly lower in adults ≥65 years of age as compared to the younger age cohort. The LBs of the two-sided 95% CI for SCRs to Afluria QIV for A/H1N1, H3N2, B/Yamagata, and B/Victoria were 47.8%, 52.8%, 42.3%, and 54.2%, respectively, in adults 18-64 years of age, and 23.7%, 23.0%, 14.2%, and 20.7%, respectively, in adults ≥65 years of age.

Reviewer comment: A pattern of lower SCRs relative to % post-vaccination HI ≥1:40 observed in both age cohorts has also been seen in study populations with high rates of influenza vaccination in the previous 12 months and where influenza vaccination is universally recommended for all persons 6 months of age and older, i.e., where a large proportion of subjects have pre-vaccination baseline HI

titers ≥1:40. Such may have been the case in CSLCT-QIV-13-01 where 87.2% of all subjects had a history of influenza vaccination, 63.3% in the prior 12 months, and >70% of all subjects had baseline HI titers ≥1:40 for A/H1N1 and A/H3N2 and >35% had baseline HI titers ≥1:40 for the B strains.

Reviewer comment: Immune responses in the elderly were generally lower as compared to adults 18-64 years of age, likely due to immunoscenesence. As previously noted, lower immune responses to influenza B strains relative to A strains have been observed in other influenza studies of elderly populations. It is not clear why SCRs for B/Yamagata were lower relative to B/Victoria in both age cohorts, particularly in the elderly.

6.1.11.3 Subpopulation Analyses

Sex

Females and males comprised 57.2% and 42.8% of the FAS, respectively. Post-vaccination GMTs, GMT ratios, SCRs and SCR differences were similar between sexes. In both males and females, Afluria QIV met NI criteria for GMT ratio and SCR differences for each of the four vaccine virus strains as compared to Afluria TIV-1 and TIV-2. Both male and female subgroups also met success criteria in the superiority analyses of GMT ratios and SCR differences for both B strains.

Reviewer comment: Differences in immune responses between males and females, including SCRs, were not statistically significant. Afluria QIV was non-inferior to Afluria TIV-1 and TIV-2 in both subgroups.

Race and Ethnicity

The majority of subjects were white (82.3%) and non-Hispanic or Latino (94.9%). Black/African American and Hispanic/Latino subjects comprised 15.8% and 4.9% of the FAS, respectively, while other racial and unreported ethnic groups were each <1% of the population. Small sample sizes precluded meaningful analyses of non-inferior and superior GMT ratios and SCR differences in racial and ethnic groups other than white and non-Hispanic/Latino subgroups. However, descriptive analyses of immune responses (GMTs, percentages of subjects with post-vaccination HI titers ≥1:40, and SCRs) were conducted for black race and Hispanic/Latino ethnicity.

Both white and non-Hispanic or Latino subgroups met success criteria for non-inferior GMT ratios and SCR differences of Afluria QIV for all four vaccine virus strains and for superiority of the alternate B strain relative to TIV.

While pre-vaccination (Day 1) GMTs in blacks or African Americans were similar to whites, post-vaccination (Day 21) GMTs in blacks or African Americans were generally higher as compared to whites across treatment groups for the four vaccine strains included in the vaccines. However, the percentages of subjects with post-vaccination HI titers ≥1:40 were generally similar between the two racial subgroups. A similar pattern of higher post-vaccination GMTs but similar percentages of post-vaccination HI titers ≥1:40 was observed in the Hispanic/Latino subgroup as compared to the non-Hispanic or Latino group. Seroconversion rates in the black/African American and Hispanic/Latino subgroups were also generally higher as compared to SCRs in the white and non-Hispanic/Latino subgroups.

Reviewer comment: Non-inferiority and superiority subgroup analyses according to sex, white race and non-Hispanic/Latino ethnicity demonstrated results similar to the overall study population. Descriptive subgroup analyses of black and Hispanic/Latino subjects showed a trend towards higher immune responses as compared to white and non-Hispanic/Latino subgroups, however, the significance of these observations is limited by the relatively small sample sizes. The very small sample sizes of other racial groups precluded meaningful analyses.

6.1.11.4 Dropouts and/or Discontinuations

Please see Sections 6.1.9, Statistical Considerations and Statistical Analysis Plan, and 6.1.10.1.3, Subject Disposition. Dropouts were not replaced and missing data not imputed. Overall, 2.8% of subjects discontinued the study, most were lost to follow-up (2.4%). This rate was similar across treatment groups and should not have significantly influenced immunogenicity results or introduced bias.

6.1.11.5 Exploratory and Post Hoc Analyses

Exploratory covariate analyses of GMTs and SCRs were conducted for age subgroups of subjects 18-49, 50-64, 65-74, and ≥75 years of age, using the 18-49 years group as a reference for comparisons. For these endpoints and for all vaccine strains, there was a trend toward lower immune responses with increasing age subgroup.

Exploratory analyses of GMT ratios and SCRs according to prior influenza vaccination indicated that, for all four vaccine virus strains, subjects vaccinated in the previous 12 months had lower immune responses than those without such a history.

Reviewer comment: Elderly subjects had lower immune responses relative to the younger age cohort and also had a higher rate of influenza vaccination within the previous 12 months (81.6% versus 45.0% for subjects 18 through 64 years). Lower immune responses are expected in the elderly due to immunosenescence. It is not clear whether previous influenza vaccination contributes to lower immune responses or whether this is an association without a causal effect.

Influenza-like illness (ILI): A total of ten subjects in the FAS reported an ILI during the study. None had laboratory-confirmed influenza infection.

6.1.12 Safety Analyses

6.1.12.1 Methods

The Safety Population, all randomized subjects (FAS) who received at least one dose of study vaccine and provided any safety follow-up data, was used to summarize all safety data. The SP was comprised of 3,449 subjects, including 1721, 864, and 864 who were vaccinated with Afluria QIV, TIV-1, and TIV-2, respectively. Data was analyzed according to the treatment received. Solicited AEs were actively collected via a diary card. Unsolicited and Serious AEs were passively collected as outlined in Section 6.1.7.

6.1.12.2 Overview of Adverse Events

Table 13 summarizes all solicited and unsolicited AEs reported in CSLCT-QIV-13-01 according to treatment group and overall.

Reviewer comment: All solicited local AEs were considered related to the study vaccines and are termed adverse reactions. Solicited systemic AEs do not always represent reactogenicity to study vaccine and, in randomized placebo-controlled trials, the frequency of these events in recipients of the investigational product may be quite similar to placebo recipients. Solicited systemic AEs in this study were assessed for relatedness and termed adverse events.

Table 13: Summary of Solicited and Unsolicited Adverse Events (Safety Population) – CSLCT-QIV-13-01

Parameter	QIV N=1721 (%)	TIV-1 N=864 (%)	TIV-2 N=864 (%)	Overall N=3449 (%)
One or more AEs	52.9	53.1	52.5	52.9
Discontinued due to AEs	0	0	0	0
Solicited local adverse reaction	37.4	34.6	36.6	36.5
Solicited systemic AEs	28.9	28.4	27.2	28.4
• Related solicited systemic AEs**	20.4	19.1	20.6	20.1
Unsolicited AEs	20.4	22.1	20.4	20.8
• Related unsolicited AEs**	3.5	2.4	2.1	2.9
¤ Related Grade 3 (severe) unsolicited AEs**	0.4	0.2	0.5	0.4
AE severity – All Solicited AEs	--	--	--	--
• Grade ≥1	46.7	45.3	45.9	46.1
• Grade 1 (mild)	42.8	41.7	40.5	41.9
• Grade 2 (moderate)	11.6	9.1	11.0	10.8
• Grade 3 (severe)	2.4	1.7	2.8	2.3
AE severity – All Unsolicited AEs	--	--	--	--
• Grade ≥1	20.3*	22.1	20.4	20.8
• Grade 1 (mild)	10.7	11.8	12.0	11.3
• Grade 2 (moderate)	9.5	11.0	8.6	9.6
• Grade 3 (severe)	4.2	3.4	3.8	3.9
Serious Adverse Events	2.3	1.6	1.5	1.9
• Related SAEs**	0.2	0	0	0
• Discontinued due to SAE	0	0	0	0
Deaths	0.3	0	0.1	0.2
Adverse Events of Special Interest	0	0	0	0

Source: STN 125254/565, Module 5, CSLCT-QIV-13-01, CSR Tables 12.2-1, 12.2-4, 12.2-5, 14.3.1.1.1, 14.3.1.7.1, and 14.3.1.9.1. STN 125254/565.17, Tables 12.2-1, 12.2-4, 14.3.1.1.1, 14.3.1.7.1, and 14.3.1.9.1
Abbreviations: QIV=Afluria QIV, TIV-1=2014-2015 US licensed Afluria TIV containing B/Yamagata, TIV-2=Afluria TIV containing the alternate B strain (B/Victoria).
*One subject in the QIV group had missing severity data for an unsolicited AE.
**Relatedness as assessed by the investigator.

Solicited Adverse Events

Solicited Local AEs

Tables 14 and 15 summarize the rates of solicited local AEs reported in the seven days following vaccination (Day 1 to Day 7) in subjects 18-64 years and ≥65 years of age, respectively. The tables present the rates of each symptom overall and for subjects who experienced Grade 3 (severe) symptoms according to treatment group.

Table 14: Solicited Local Adverse Reactions, Overall and Grade 3, Subjects 18 through 64 Years of Age, Day 1 to Day 7 Post-Vaccination (Safety Population) – CSLCT-QIV-13-01

Local Solicited AE	Maximum Severity Grade	QIV N=854 n(%)	TIV-1 N=428 n(%)	TIV-2 N=430 n(%)	Overall N=1712 n(%)
Any Local AE	Overall[1]	413 (48.4)	189 (44.2)	221 (51.4)	823 (48.1)
Any Local AE	Grade 3[2]	7 (0.8)	6 (1.4)	5 (1.2)	18 (1.1)
Pain	Overall[1]	409 (47.9)	187 (43.7)	218 (50.7)	814 (47.5)
Pain	Grade 3[2]	6 (0.7)	6 (1.4)	5 (1.2)	17 (1.0)
Redness	Overall[1]	25 (2.9)	12 (2.8)	12 (2.8)	49 (2.9)
Redness	Grade 3[2]	0	0	0	0
Swelling/lump	Overall[1]	32 (3.7)	10 (2.3)	15 (3.5)	57 (3.3)
Swelling/lump	Grade 3[2]	1 (0.1)	0	1 (0.2)	2 (0.1)

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 14.3.1.2.2.
[1]n represents the number of subjects in each treatment group within the age cohort 18-64 years who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Safety Population for the treatment group within the age cohort 18-64 years.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: QIV n=846; TIV-1 n=422-423; TIV-2 n=426; Overall n=1694-1695.

Table 15: Solicited Local Adverse Reactions, Overall and Grade 3, Subjects ≥65 Years of Age, Day 1 to Day 7 Post-Vaccination (Safety Population) – CSLCT-QIV-13-01

Local Solicited AE	Maximum Severity Grade	QIV N=867 n(%)	TIV-1 N=436 n(%)	TIV-2 N=434 n(%)	Overall N=1737 n(%)
Any Local AE	Overall[1]	231 (26.6)	110 (25.2)	95 (21.9)	436 (25.1)
Any Local AE	Grade 3[2]	5 (0.6)	0	2 (0.5)	7 (0.4)
Pain	Overall[1]	213 (24.6)	99 (22.7)	91 (21.0)	403 (23.2)
Pain	Grade 3[2]	1 (0.1)	0	1 (0.2)	2 (0.1)
Redness	Overall[1]	36 (4.2)	9 (2.1)	11 (2.5)	56 (3.2)
Redness	Grade 3[2]	3 (0.3)	0	1 (0.2)	4 (0.2)
Swelling/lump	Overall[1]	28 (3.2)	8 (1.8)	7 (1.6)	43 (2.5)
Swelling/lump	Grade 3[2]	4 (0.5)	0	0	4 (0.2)

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 14.3.1.2.2.
[1]n represents the number of subjects in each treatment group within the age cohort ≥65 years who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Safety Population for the treatment group within the age cohort ≥65 years.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period: QIV n=865; TIV-1 n=431; TIV-2 n=432; Overall n=1728.

Reviewer comment: The solicited AE of "swelling/lump" was described as an endpoint of "induration/swelling" in the study protocol, CSR, and SAP and in the toxicity grading scales. The term "swelling/lump" appeared on the subject diary card and on the CRF. The terms are used interchangeably in this review.

A total of 37.4% of subjects overall experienced solicited local adverse reactions after vaccination with Afluria QIV as compared to similar rates following TIV-1 (34.6%) or TIV-2 (36.6%). In the 18-64 years age cohort, a total of 48.4% reported solicited local adverse reactions following QIV, mostly pain (47.9%) followed by swelling/lump (3.7%) or redness (2.9%). Rates were similar across treatment groups. Most reactions were Grade 1 or Grade 2 (mild to moderate). Less than 1% of QIV recipients reported Grade 3 (severe) reactions as compared to 1.4% and 1.2% of TIV-1 and TIV-2 recipients. Local reactions in the 18-64 years age cohort began on Day 1 in the majority of subjects who reported reactions and had a mean duration ranging from 2.0 to 3.0 days, similar across treatment groups.

Subjects ≥65 years of age reported fewer solicited local adverse reactions overall (26.6%) after receiving Afluria QIV as compared to the younger age cohort, primarily

pain (24.6%) followed by redness (4.2%) or swelling/lump (3.2%). The rates of local reactions following Afluria QIV in this age group, however, were slightly higher as compared to TIV: pain (21.0%-22.7%), redness (2.1%-2.5%), and swelling/lump (1.6%-1.8%). Most reactions were Grade 1 or Grade 2 (mild to moderate). Grade 3 (severe) reactions occurred in less than 1% of subjects for all parameters across treatment groups. Local reactions in the ≥65 years age cohort began on Day 1 in the majority of subjects who reported reactions and had a mean duration ranging from 1.6 to 3.6 days, similar across treatment groups

Reviewer comment: Rates, severity, and duration of local injection site reactions were not unusual for an inactivated influenza vaccine (IIV). As has been observed in other studies of IIVs, older adults experienced less local reactogenicity than younger adults. Afluria QIV caused slightly more local reactogenicity as compared to TIV in adults ≥65 years of age but was not notably more reactogenic than TIV in younger adults. A total of 1.1% and 0.4% of subjects 18-64 years and ≥65 years, respectively, experienced Grade 3 (severe) measured injection site reactions. Due to concerns raised by post-marketing reports, severe cellulitis-like injection site reactions were specifically evaluated in this study and are discussed in greater detail later in this section.

Solicited Systemic Adverse Events

Tables 16 and 17 summarize the rates of solicited systemic AEs reported in the seven days following vaccination (Day 1 to Day 7) in subjects 18-64 years and ≥65 years of age, respectively. The tables present the rates of each symptom overall and for subjects who experienced Grade 3 (severe) symptoms according to treatment group.

Table 16: Solicited Systemic Adverse Events, Overall and Grade 3, Subjects 18-64 Years of Age, Day 1 to Day 7 Post-Vaccination (Safety Population) – CSLCT-QIV-13-01

Systemic Solicited AE	Maximum Severity Grade	QIV N=854 n(%)	TIV-1 N=428 n(%)	TIV-2 N=430 n(%)	Overall N=1712 n(%)
Any Systemic AE	Overall[1]	327(38.3)	156(36.4)	154(35.8)	637(37.2)
Any Systemic AE	Grade 3[2]	29(3.4)	9(2.1)	13(3.1)	51(3.0)
Headache	Overall[1]	185(21.7)	65(15.2)	82(19.1)	332(19.4)
Headache	Grade 3[2]	14(1.7)	4(0.9)	5(1.2)	23(1.4)
Malaise	Overall[1]	76(8.9)	39(9.1)	40(9.3)	155(9.1)
Malaise	Grade 3[2]	6(0.7)	0	3(0.7)	9(0.5)
Muscle ache/Myalgia	Overall[1]	218(25.5)	100(23.4)	104(24.2)	422(24.6)
Muscle ache/Myalgia	Grade 3[2]	16(1.9)	6(1.4)	5(1.2)	27(1.6)
Chills	Overall[1]	41(4.8)	19(4.4)	20(4.7)	80(4.7)
Chills	Grade 3[2]	5(0.6)	1(0.2)	2(0.5)	8(0.5)
Nausea	Overall[1]	59(6.9)	33(7.7)	27(6.3)	119(7.0)
Nausea	Grade 3[2]	5(0.6)	2(0.5)	5(1.2)	12(0.7)
Vomiting	Overall[1]	13(1.5)	4(0.9)	10(2.3)	27(1.6)
Vomiting	Grade 3[2]	3(0.4)	0	3(0.7)	6(0.4)
Fever	Overall[1]	9(1.1)	4(0.9)	2(0.5)	15(0.9)
Fever	Grade 3[2]	3(0.4)	0	0	3(0.2)

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 14.3.1.3.2.
[1]n represents the number of subjects in each treatment group within the age cohort 18-64 years who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Safety Population for the treatment group within the age cohort 18-64 years.

[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period. Ranges for denominators in each treatment group (except for fever) were as follows: QIV n=843-845; TIV-1 n=424-425; TIV-2 n=425-426; Overall n=1693-1696.
[3]Grade 3 Fever defined as ≥39.0°C or ≥102.2°F. Denominators for fever: QIV n=841; TIV-1 n=422; TIV-2 n=425; Overall n=1688.

Table 17: Solicited Systemic Adverse Events, Overall and Grade 3, Subjects ≥65 Years of Age, Day 1 to Day 7 Post-Vaccination (Safety Population) – CSLCT-QIV-13-01

Systemic Solicited AE	Maximum Severity Grade	QIV N=867 n(%)	TIV-1 N=436 n(%)	TIV-2 N=434 n(%)	Overall N=1737 n(%)
Any Systemic AE	Overall[1]	171(19.7)	89(20.4)	81(18.7)	341(19.6)
Any Systemic AE	Grade 3[2]	6(0.7)	5(1.2)	7(1.6)	18(1.0)
Headache	Overall[1]	73(8.4)	31(7.1)	34(7.8)	138(7.9)
Headache	Grade 3[2]	0	1(0.2)	3(0.7)	4(0.2)
Malaise	Overall[1]	38(4.4)	22(5.0)	22(5.1)	82(4.7)
Malaise	Grade 3[2]	4(0.5)	1(0.2)	1(0.2)	6(0.3)
Muscle ache/Myalgia	Overall[1]	110(12.7)	61(14.0)	53(12.2)	224(12.9)
Muscle ache/Myalgia	Grade 3[2]	3(0.3)	3(0.7)	2(0.5)	8(0.5)
Chills	Overall[1]	17(2.0)	9(2.1)	6(1.4)	32(1.8)
Chills	Grade 3[2]	0	2(0.5)	1(0.2)	3(0.2)
Nausea	Overall[1]	14(1.6)	8(1.8)	9(2.1)	31(1.8)
Nausea	Grade 3[2]	0	0	1(0.2)	1(0.1)
Vomiting	Overall[1]	4(0.5)	0	3(0.7)	7(0.4)
Vomiting	Grade 3[2]	1(0.1)	0	1(0.2)	2(0.1)
Fever	Overall[1]	2(0.2)	4(0.9)	2(0.5)	8(0.5)
Fever	Grade 3[2]	0	0	1(0.2)	1(0.1)

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 14.3.1.3.2.
[1]n represents the number of subjects in each treatment group within the age cohort ≥65 years who experienced symptoms even if severity grades were missing; denominator for percentage is number of subjects in the Safety Population for the treatment group within the age cohort ≥65 years.
[2]Denominator for the percentage excludes subjects in each treatment group who were missing severity data for all 7 days of the solicited AE period. Ranges for denominators in each treatment group (except for fever) were as follows: QIV n=865; TIV-1 n=431-432; TIV-2 n=431; Overall n=1727-1728.
[3]Grade 3 Fever defined as ≥39.0°C or ≥102.2°F. Denominators for fever: QIV n=863; TIV-1 n=431; TIV-2 n=429; Overall n=1723.

A total of 28.9% of subjects overall experienced solicited systemic AEs after vaccination with Afluria QIV as compared to similar rates following TIV-1 (28.4%) or TIV-2 (27.2%). In the 18-64 years age cohort, 38.3% of subjects reported solicited systemic AEs following QIV, primarily muscle ache/myalgia (25.5%), headache (21.7%), malaise (8.9%), nausea (6.9%) and chills (4.8%). Rates were similar across treatment groups. Fever was uncommon, 0.9% across treatment groups. However, three recipients (0.4%) of QIV experienced Grade 3 (severe) fever as compared to none of the recipients of TIV. Most solicited systemic events were Grade 1 or Grade 2 (mild to moderate). A total of 3.4% of QIV recipients reported Grade 3 (severe) reactions as compared to 2.1% and 3.1% of TIV-1 and TIV-2 recipients, respectively.

In the ≥65 years age cohort, 19.7% of subjects reported solicited systemic AEs following QIV, primarily muscle ache/myalgia (12.7%), headache (8.4%), and malaise (4.4%). Rates were similar across treatment groups. Fever was uncommon, 0.5% across treatment groups. One recipient (0.2%) of TIV-2 experienced Grade 3 (severe) fever as compared to none in the other two treatment groups. Most solicited systemic events were Grade 1 or Grade 2 (mild to moderate). A total of 0.7% of QIV recipients reported

Grade 3 (severe) reactions as compared to 1.2% and 1.6% of TIV-1 and TIV-2 recipients, respectively.

In both age cohorts overall, most solicited systemic symptoms began between Day 1 and Day 3, and persisted for a mean duration of 1.1 to 2.2 days.

Reviewer comment: Other than slightly more reports of fever in recipients of Afluria QIV as compared to TIV in adults 18-64 years of age (9 versus 6), the quadrivalent vaccine was not associated with higher rates of solicited systemic AEs. Overall, younger adults 18-64 years of age reported more systemic symptoms than adults ≥65 years of age (37.2% versus 19.6%). Most (20.1% ÷ 28.4% = 70.8%) systemic events were assessed as being related to the study vaccines, however, there was no placebo group for comparison.

Subpopulation Analyses of Solicited Adverse Events

Females reported more solicited injection site reactions overall as compared to males (41.7% versus 29.5%). Females in the Afluria QIV group were more likely to report any local reaction and injection site pain as compared to TIV recipients (44.0% versus 38.1% and 41.0%; 42.0% versus 36.0% and 39.6%, respectively). Differences in local reactogenicity among treatment groups were less apparent in males, however, more male Afluria QIV recipients experienced swelling/lump as compared to TIV (1.7% versus 0.6% and 1.1%). Overall, more females than males experienced solicited systemic symptoms (32.5% versus 22.7%). The largest imbalances in females versus males, respectively, occurred for headache (17.0% versus 9.0%), myalgia (20.6% versus 16.3%), and malaise (8.1% versus 5.2%). No significant differences in the rates of solicited systemic AEs were noted among treatment groups within gender subgroups.

A total of 32.5% of black/African American subjects experienced solicited injection site reactions as compared to 37.3% of whites. More black/African American recipients of Afluria QIV experienced injection site swelling/lump than TIV recipients (4.0% versus 0.8%). Significant differences in local reactogenicity were not apparent among treatment groups in white subjects. A total of 30.8% of black/African American subjects experienced solicited systemic symptoms as compared to 27.9% of white subjects. No large imbalances were observed for specific solicited systemic symptoms between these two racial groups or among treatment groups within racial subgroups. Small sample sizes precluded meaningful analyses of other racial subgroups.

Overall, more subjects in the Hispanic/Latino subgroup experienced solicited local reactogenicity than non-Hispanic/Latinos (42.4% versus 36.3%). No large imbalances occurred among treatment groups within the Hispanic/Latino subgroup. Among non-Hispanic/Latinos, rates of solicited local injection site reactions overall and for pain were similar among treatment groups. Swelling occurred with greater frequency in the Afluria QIV group as compared to TIV (3.5% versus 2.5% and 1.9%). Hispanic/Latinos had more solicited systemic symptoms overall, headache, and myalgia (34.5%, 18.8%, and 24.8%, respectively) as compared to non-Hispanic/Latinos (28.1%, 13.4%, and 18.4%, respectively). No large imbalances in systemic symptoms were observed among treatment groups.

Reviewer comment: Subpopulations analyses revealed an overall trend towards greater local reactogenicity in females as compared to males, Hispanic/Latinos as compared to non-Hispanic/Latinos, and in recipients of Afluria QIV versus TIV.

Other than greater overall solicited systemic symptoms including headache and myalgia among females versus males and Hispanic/Latinos versus non-Hispanic/Latinos, no large imbalances in systemic reactogenicity were observed among subpopulations.

Injection Site Cellulitis, Cellulitis-like Reaction, or Grade 3 Induration/Swelling

In 2011, Seqirus received increased postmarketing reports from its worldwide surveillance of severe cellulitis-like injection site reactions associated with administration of Afluria TIV. Detailed review by the Applicant and FDA indicated that many cases were associated with concomitant administration of other vaccines, e.g., pneumococcal vaccine, and that the increase in reports may have been due in part to hyperstimulated reporting following the SH 2010 increase in febrile seizures associated with Afluria TIV. An OBE/DE review of VAERS data found no increase in reports of severe or serious injection site reactions associated with Afluria as compared to other TIV's, and the numbers of postmarketing reports received by the Applicant following 2011 have since returned to baseline levels. (please see the clinical reviews of STN 125254/440.1 and 440.2 for further information). Nevertheless, due to concerns for a potential increase in local reactogenicity with the addition of a second B strain antigen to the formulation, monitoring of severe (Grade 3) induration/swelling, cellulitis-like reactions, and cellulitis at the injection site was a pre-specified safety endpoint in CSLCT-QIV-13-01.

A total of six subjects, five recipients of Afluria QIV (n=1721, 0.3%) and one recipient of Afluria TIV-2 (n=864, 0.1%), experienced Grade 3 (severe) injection site swelling/lump during the study. All of the reactions began within four days of vaccination and resolved within five days. Maximum measured induration ranged from 100 to 120 mm. One subject sought medical advice but received no specific treatment. No reactions were assessed as serious. Of the six subjects, four were ≥65 years of age, two were male, four were female, one was black, five were white, and all were non-Hispanic/non-Latino. No subject experienced a cellulitis-like or cellulitis at the injection site during the study.

Reviewer comment: Although the number of subjects who experienced severe injection site swelling in the study was low (n=6, 0.17%), there was an imbalance between severe injection site swelling in subjects treated with Afluria QIV (0.3%) as compared to recipients of Afluria TIV-1/TIV-2 (n=1728, 0.06%). Whether this was due to chance or to greater reactogenicity related to an additional B strain antigen is not clear. In their scientific investigation of febrile seizures and AEs in children and adolescents associated with administration of the SH 2010 formulation of Afluria TIV, the Applicant noted that the B strain was associated with greater proinflammatory cytokines than A strains and subsequently [redacted] with the aim of reducing proinflammatory cytokines and pyrogenicity. The PI was modified in 2012 to include cellulitis and large injection site swelling in Section 6.2, postmarketing adverse experience. The Applicant has implemented ongoing postmarketing surveillance specifically for such reactions. We will monitor for increased reports following approval of Afluria QIV.

Reviewer comment: With this supplement, we will grant approval of Afluria QIV for use with the PharmaJet jet injector (JI). Because clinical trials demonstrated that administration of Afluria TIV by JI was associated with more injection site reactions as compared to administration by needle and syringe (please see the

Afluria PI), we will also keep in mind the potential for a further increase in local reactogenicity if Afluria QIV is administered by JI.

Unsolicited Adverse Events (Day 1 through Day 28)
Only treatment emergent AEs (TEAE), i.e., those that began or were exacerbated after exposure to study treatment, were included in the analyses of unsolicited AEs. Multiple occurrences of the same AE were counted once per subject. AEs were coded according to MedDRA preferred term (PT) and system organ class (SOC), version 17. Please see Table 13 for an overview of unsolicited AEs, and CSLCT-QIV-13-01 CSR Tables 12.2-4, 12.2-5, 14.3.1.7.1, 14.3.1.9.1, 14.3.1.7.2, and 14.3.1.9.2 for detailed summaries of unsolicited AEs by PTs and SOCs reported in each treatment group according to age cohorts ≥18 years, 18-64 years, and ≥65 years.

A total of 719 subjects (20.8%) ≥18 years of age reported 1343 spontaneous or unsolicited AEs in the 28 days following vaccination, with similar proportions across treatment groups: Afluria QIV (20.4%), TIV-1 (22.1%), and TIV-2 (20.4%). System Organ Class categories with the highest overall rates of AEs were: Musculoskeletal and Connective Tissue Disorders (5.0%), primarily back pain (1.7%); Nervous System Disorders (5.0%), primarily headache (3.5%); Respiratory, Thoracic, and Mediastinal Disorders (4.4%), primarily oropharyngeal pain (1.8%), rhinorrhea (1.2%), cough (1.0%), and nasal congestion (1.0%); Infections and Infestations (3.9%), primarily nasopharyngitis (0.9%); Gastrointestinal Disorders (3.5%), primarily diarrhea (1.2%); and General Disorders and Administration Site Conditions (2.3%), primarily fatigue (0.5%). None of the AEs resulted in discontinuation from the study.

Among recipients of Afluria QIV 18-64 years of age, the most common unsolicited AEs (frequency ≥1%) were: headache (5.3%), oropharyngeal pain (2.5%), back pain (1.9%), diarrhea (1.6%), cough (1.3%), and nausea (1.1%). Among recipients of Afluria QIV ≥65 years of age, the most common unsolicited AEs (frequency ≥1%) were: headache (2.3%, rhinorrhea (1.3%), oropharyngeal pain (1.2%), and back pain (1.2%). The overall frequencies of unsolicited AEs were similar across treatment groups and between age cohorts. There was a small trend towards more nervous system disorders and respiratory tract disorders in subjects 18-64 years of age as compared to the older age cohort (5.9% and 4.7% versus 4.0% and 4.1%, respectively) and more cardiac disorders in subjects ≥65 years of age as compared to the younger age cohort (1.1% versus 0.1%, respectively, data not shown in table for the latter cohort). However, no large imbalances or unusual patterns of individual events (PT) were observed either across age or treatment groups.

Reviewer comment: Rates of unsolicited AEs were generally low, mild to moderate in severity, and similar across treatment groups and age cohorts. Slightly higher percentages of subjects in the Afluria QIV group reported severe AEs as compared to TIV (4.2% versus 3.4% and 3.8% for TIV-1 and TIV-2, respectively; please see the next section). However, Afluria QIV was not associated with unusual patterns or large imbalances relative to the TIV comparators. Only one subject (Afluria QIV 18-64 age group) in the safety population overall was missing severity grade data for unsolicited AEs.

<u>Severity and Relatedness of Unsolicited Adverse Events</u>
Among all subjects, a total of 11.3%, 9.6%, and 3.9% reported unsolicited AEs of mild (Grade 1), moderate (Grade 2), or severe (Grade 3) intensity, respectively. Severity

grades were similar across treatment groups. Among the 1721 recipients of Afluria QIV in both age cohorts, a total of 10.7%, 9.5%, and 4.2% reported unsolicited AEs of mild, moderate, and severe intensity, respectively. In comparison, a total of 3.4% and 3.8% of TIV-1 and TIV-2 recipients among subjects in both age cohorts, respectively, reported severe unsolicited AEs. Overall, a total of 3.5% of Afluria QIV recipients were assessed by the investigator as having unsolicited AEs related to the study vaccine as compared to 2.4% and 2.1% of TIV-1 and TIV-2 recipients, respectively. [Data derived from CSLCT-QIV-13-01 CSR Tables 14.3.1.9.1 and 14.3.1.9.2.]

A total of 73 (4.2%) recipients of Afluria QIV experienced 101 severe events. Of these subjects, 30 (3.5%) were 18-64 years of age [38 severe events, 4 (0.5%) assessed as related] and 43 (5.0%) were ≥65 years [63 severe events, 3 (0.3%) assessed as related]. In comparison, 29 (3.4%) TIV-1 and 33 (3.8%) TIV-2 subjects experienced 37 and 46 severe AEs, respectively. Two recipients of TIV-1 (0.2%) and four recipients (0.5%) of TIV-2 had 2 and 11 AEs assessed as related, respectively. Evaluation of the electronic datasets yielded unsolicited AE results consistent with the CSR text, tables (14.3.1.9.1 and 14.3.1.9.2), and listing (16.2.7.1.1).

The electronic datasets and subject listings were evaluated for subjects who experienced severe (Grade 3) unsolicited AEs. Eight, two, and one severe AE in the QIV, TIV-1, and TIV-2 groups, respectively, were also SAEs and are discussed in Sections 6.1.12.3 and 6.1.12.4 of this review. Of the non-serious severe AEs, nine events in six QIV recipients were considered related to study vaccine: bronchitis, sinusitis, myalgia, cough, upper respiratory tract congestion, diarrhea, abdominal pain upper, oropharyngeal pain, and dysmenorrhea. In the opinion of the reviewer, only diarrhea (onset 4 days post-vaccination) and oropharyngeal pain (onset 9 days post-vaccination) appeared possibly (but unlikely) related to study vaccine while the remainder appeared unrelated due to lack of close temporal relationship and/or biological plausibility. Among TIV-1 and TIV-2 recipients, six subjects experienced thirteen non-serious severe AEs assessed as related to study vaccine: arthralgia (knee pain), oropharyngeal pain (n=2), headache (n=2), cough, rhinorrhea (n=2), sneezing, nasal congestion, pain, pharyngitis streptococcal, and pyrexia. In the opinion of the reviewer, only one event, oropharyngeal pain (onset 1 day post-vaccination) appeared possibly related to study vaccine due to the close temporal relationship.

One other subject (TIV-2 subject # 8400307-0001) experienced a severe AE of cellulitis seven days post-vaccination that was not considered related to study vaccine but for which additional information was requested on December 15, 2015. In response to our request (STN 125254/565.1), the Applicant indicated that the subject was a 62 year old female with a history of chronic lower extremity edema, type 2 diabetes and chronic obstructive pulmonary disease. Although the subject's CRF does not specify the location of her AE of cellulitis, she specifically denied any pain, redness, or induration/swelling at the left deltoid vaccination site, fever, or any other solicited systemic symptoms from Day 1 through Day 7 post-vaccination. Her cellulitis began on Day 8 (seven days post-vaccination), was not serious, and was treated with oral ciprofloxacin and trimethoprim sulfamethoxazole. The outcome was "not recovered or resolved". No medical evaluation or microbiological studies were reported as having been obtained.

Reviewer comment: The reviewer agrees that this case of cellulitis does not appear related to the study vaccine.

Reviewer comment: Although more QIV recipients experienced severe unsolicited AEs as compared to TIV recipients, most of the events in all three treatment groups appeared unrelated to study vaccine.

Subpopulation Analyses of Unsolicited AEs

No significant differences were observed in the overall rates of unsolicited AEs among subjects in the age subgroups 18-49, 50-64, 65-74, and ≥75 years. However, the proportion of events assessed as related to study vaccine trended downward with advancing age: 18-49 years (5.0%), 50-64 years (2.8%), 65-74 years (3.3%), ≥75 years (2.1%).

A higher proportion of females experienced unsolicited AEs as compared to males (23.5% versus 17.1%). The largest differences in the rates of reported unsolicited AEs between females and males, respectively, as categorized by system organ class and preferred term were: nervous system disorders (6.1% vs 3.4%), primarily headache (4.4% vs 2.3%), musculoskeletal and connective tissue disorders (5.7% vs 4.1%), primarily back pain (2.0% vs 1.2%), respiratory, thoracic, and mediastinal disorders (4.8% vs 3.9%), primarily oropharyngeal pain (2.3% vs 1.1%), infections and infestations (4.6% vs 2.9%), primarily nasopharyngitis (1.0% vs 0.7%), and gastrointestinal disorders (4.2% vs 2.5%), primarily diarrhea (2.0% vs 0.6%). No large differences in the severity or relatedness of AEs were observed between the sexes.

Sub-analyses of racial and ethnic groups demonstrated a trend towards lower proportions of black/African American subjects as compared to whites (16.4% versus 21.8%) and Hispanic/Latinos as compared to Non-Hispanic/Latinos (17.6% versus 21.0%) who experienced unsolicited AEs. However, the proportions of subjects who had unsolicited AEs assessed as related were higher in blacks/African Americans as compared to whites (4.7% versus 2.6%) and in Hispanic/Latinos as compared to non-Hispanic/Latinos (6.3% versus 3.4%). The significance of these differences is not clear. No large differences were observed among treatment groups within these racial and ethnic subgroups. The small sample sizes of other racial groups precluded meaningful sub-analyses of unsolicited AEs.

6.1.12.3 Deaths

Six subjects died during the study period, five in the Afluria QIV group and one in the Afluria TIV-2 group. Table 18 summarizes deaths by MedDRA preferred term and relationship to vaccination as assessed by the investigator.

Table 18: Summary of Deaths following Study Vaccination (Safety Population) – CSLCT-QIV-13-01

Group	Subject ID	Age/ Sex	Preferred Term	Onset*	Death*	Relationship**
QIV	8400283-0041	33M	Road traffic accident	[redacted]	[redacted]	Not related
QIV	8400297-0055	71M	Pneumonia	2	[redacted]	Related
QIV	8400283-0075	65F	Cardiac failure	[redacted]	[redacted]	Not related
QIV	8400294-0093	74M	Acute myocardial infarction	[redacted]	[redacted]	Not related
QIV	8400310-0104	79M	Ventricular arrhythmia	[redacted]	[redacted]	Not related
TIV-2	8400302-0118	78F	Sepsis	[redacted]	[redacted]	Not related

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 12.3-1, Narratives Section 14.3.3, and electronic datasets.
*Number of days post-vaccination

**Relationship as assessed by the investigator

- Subject 8400283-0041 was a 33 year old African American male who reported no past medical history, took no concomitant medications, and had never received influenza vaccination. [redacted] days post-vaccination (Study Day [redacted]) with Afluria QIV, the subject was in a severe motor vehicle accident and died. The Applicant did not know whether an autopsy was performed. The investigator and Applicant assessed the death as not related to study vaccine.
- Subject 8400283-0075 was a 65 year old white female with a past medical history of hypertension, hypothyroidism, and osteoarthritis. At [redacted] days post-vaccination (Study Day [redacted]) with Afluria QIV, the subject was walking and fell over due to a sudden cardiac event, and died. Emergency medical technicians were unable to resuscitate her. No autopsy was performed. The investigator and Applicant assessed the death as not related to study vaccine.
- Subject 8400294-0093 was a 74 year old white male with a history of hypertension, hypercholesterolemia, and hypothyroidism who had last received influenza vaccine in October 2013. At [redacted] days post-vaccination (Study Day [redacted]) with Afluria QIV, the subject had an acute myocardial infarction and died at home. No autopsy or tests were performed. The investigator and Applicant assessed the death as not related to study vaccine.
- Subject 8400297-0055 was a 71 year old white male with multiple medical problems including ex-smoker, type 2 diabetes, hypercholesterolemia, hypertriglyceridemia, hypertension, hypothyroidism, pancreatitis, gastroesophageal reflux disease (GERD), sleep apnea, pneumonia (2011), peripheral neuropathy, vitamin D deficiency, cholecystectomy, appendectomy, and hernia repair, who last received influenza vaccine in October 2013. On July 16, 2014, the subject presented to his primary care provider (PCP) with shortness of breath. CXR revealed pulmonary infiltrates, a question of pulmonary fibrosis, and possible pneumonia. A chest CT was recommended but the patient did not follow up. On August 24, 2014, the patient received Afluria QIV. Examination prior to vaccination revealed normal temperature, clear lungs, and no apparent distress. The subject did not disclose the episode of shortness of breath five weeks earlier. On August 26, 2014, the subject returned to the study site with cough and temperature 98.5°F, and was evaluated for ILI which included nasal/throat swabs for influenza. He was referred to his PCP for treatment, had a CXR that same day which showed pneumonia, and was started on levofloxacin 500mg daily, an albuterol inhaler for wheezing, and prednisone (Aug 26-28). On August 28, 2014, the patient was hospitalized with community-acquired multilobar pneumonia and respiratory failure requiring mechanical ventilation. Tests for influenza were negative. His pneumonia was treated with intravenous antibiotics including ceftriaxone, doxycycline, linezolid, and imipenem without improvement. The hospital course was further complicated by right pneumothorax, multifocal cerebrovascular infarcts, deep vein thrombosis, gastrointestinal bleeding, acute renal insufficiency, and the acute respiratory distress syndrome (ARDS). He remained unresponsive and ventilator dependent with a very poor prognosis. The family opted for palliative care and the patient was allowed to expire on [redacted] days post-vaccination). The hospital discharge summary did not provide results of microbiological studies.

  The investigator assessed the event as possibly related to the study vaccine because of the close temporal relationship citing a possible mechanism of

idiosyncratic inflammatory or immune response to any of the vaccine components contributing to respiratory compromise in a patient with pre-existing lung disease. The Applicant assessed the event as not related to study vaccine despite the temporal relationship, citing the undiagnosed underlying lung disease and respiratory symptoms five weeks prior to vaccination, and other multiple risk factors for severe complicated community acquired pneumonia and a poor prognosis. Additionally, an acute idiosyncratic inflammatory response or hypersensitivity reaction to vaccination would normally involve multiple organ systems at initial presentation rather than being isolated to the lungs.

Reviewer comment: This subject had an underlying undiagnosed subacute pulmonary process, possibly fibrosis or pneumonia, prior to vaccination. He appeared to have either a progressive infection or a new superimposed acute pneumonia, and had multiple risk factors for a poor outcome including his advanced age, diabetes, and cardiovascular disease. It is not possible to prove that vaccination did not trigger an inflammatory response that exacerbated the underlying pulmonary process. However, in the opinion of this reviewer, it seems more likely that the timing of vaccination was coincidental and that his advanced age, diabetes, and other co-morbidities may have contributed to his poor outcome.

- Subject 8400310-0104 was a 79 year old white male with a past medical history that included coronary artery disease, myocardial infarction, coronary angioplasty, hypertension, hypercholesterolemia, chronic obstructive pulmonary disease, GERD, type 2 diabetes, and depression. At [redacted] days post-vaccination (Study Day [redacted]) with Afluria QIV, the subject developed a severe ventricular dysrhythmia and died. The investigator and Applicant assessed the event as related to his extensive cardiovascular disease and not related to study vaccine.
- Subject 8400302-0118 was a 78 year old female with a past medical history of aortic stenosis, aortic stent insertion in 2014, rheumatoid arthritis, multiple drug allergies, and prior influenza vaccination in September 2013. At [redacted] days post-vaccination (Study Day [redacted]) with Afluria TIV-2, she developed a severe pneumonia with sepsis syndrome and was admitted to an intensive care unit (ICU) where she had a cardiac arrest and died that same day. The investigator and Applicant assessed the event as not related to study vaccine.

Reviewer comment: Six of the six deaths associated with study vaccination appeared unrelated to the study vaccines due to lack of a close temporal relationship and/or lack of biological plausibility. For reasons already stated, Afluria QIV does not appear to have contributed directly or significantly to the fatal case of severe multilobar pneumonia and multiple organ system failure (Subject 8400297-0055).

6.1.12.4 Nonfatal Serious Adverse Events

In the 180 days following vaccination, a total of 66 subjects in the Safety Population (1.9%) experienced 89 SAEs. Of these, 49 SAEs were reported by 39 of 1721(2.3%) subjects in the Afluria QIV group. In comparison, 14 of 864 (1.6%) Afluria TIV-1 recipients experienced a total of 20 SAEs and 13 of 864 (1.5%) Afluria TIV-2 recipients experienced a total of 20 SAEs. Table 19 summarizes SAEs, including deaths, that occurred from Day 1 through Day 180 categorized by MedDRA SOC and treatment

group. More subjects ≥65 years (3.0%) had SAEs as compared to subjects 18-64 years (0.8%). The most common SAEs occurred in the following SOC categories: Cardiac Disorders (0.5% of subjects ≥18 years), Infections and Infestations (0.3%), and Nervous System Disorders (0.3%). No SAE within a specific MedDRA PT or SOC category occurred in more than 3 subjects (0.1%) with the exception of atrial fibrillation which occurred in 6 subjects (0.2%) overall (including 5 subjects ≥65 years). No large imbalances were observed among treatment groups.

Table 19: Frequency of Serious Adverse Events According to MedDRA System Organ Class and Treatment Group – Adults ≥18 Years of Age (Safety Population) – CSLCT-QIV-13-01

System Organ Class	QIV N=1721 n(%)	TIV-1 N=864 n(%)	TIV-2 N=864 n(%)	Overall N=3449 n(%)
≥1 SAE – ≥18 years*	39 (2.3)	14 (1.6)	13 (1.5)	66 (1.9)
≥1SAE – 18-64 years*	6 (0.7)	4 (0.9)	4 (0.9)	14 (0.8)
≥1 SAE - ≥65 years*	33 (3.8)	10 (2.3)	9 (2.1)	52 (3.0)
Infections and infestations	2 (0.1)	8 (0.9)	1 (0.1)	11 (0.3)
Neoplasms, benign, malignant	4 (0.2)	1 (0.1)	2 (0.2)	7 (0.2)
Metabolism and nutrition disorders	1 (0.1)	0	0	1 (0.0)
Psychiatric disorders	0	0	2 (0.2)	2 (0.1)
Nervous system disorders	8 (0.5)	2 (0.2)	2 (0.2)	12 (0.3)
Cardiac disorders	10 (0.6)	2 (0.2)	5 (0.6)	17 (0.5)
Vascular disorders	4 (0.2)	0	0	4 (0.1)
Respiratory, thoracic, and mediastinal disorders	3 (0.2)	0	4 (0.5)	7 (0.2)
Gastrointestinal disorders	5 (0.3)	0	0	5 (0.1)
Skin and subcutaneous tissue disorders	0	1 (0.1)	0	1 (0.0)
Musculoskeletal and connective tissue disorders	2 (0.1)	1 (0.1)	1 (0.1)	4 (0.1)
Renal and urinary disorders	1 (0.1)	3 (0.3)	0	4 (0.1)
General disorders and administration site conditions	3 (0.2)	0	1 (0.1)	4 (0.1)
Investigations	0	1 (0.1)	0	1 (0.0)
Injury, poisoning, and procedural complications	3 (0.2)	0	1 (0.1)	4 (0.1)

Source: Adapted from Module 5, CSLCT-QIV-13-01 CSR, Table 14.3.1.10.1 and 14.3.1.10.2.
*Percentages based on total Safety Population subjects ≥18 years and older.

Reviewer comment: As anticipated, more subjects in the older age cohort ≥65 years [n=52 (3.0%)] experienced SAEs as compared to younger adults 18-64 years of age [n=14 (0.8%)]. Overall, more Afluria QIV recipients experienced SAEs (2.3%) versus the comparators TIV-1 (1.6%) and TIV-2 (1.5%). However, no large imbalance or unusual patterns of specific events were observed across treatment groups.

Table 20 summarizes the 15 SAEs experienced by 12 subjects during the active study period, Day 1 through Day 28 by age cohort and treatment group. During the entire study period, 4 SAEs in 3 recipients of Afluria QIV were considered related to the study vaccine, all occurring within 28 days of vaccination. Brief narratives are provided for events assessed as related to study vaccine by the investigator and/or Applicant or those identified as being of special interest by the reviewer. Please see Section 6.1.12.3 for a review of deaths reported in the study.

Table 20: SAEs Day 1 through Day 28 by Treatment, Age Cohort, and Subject (Safety Population) – CSLCT-QIV-13-01

Arm	Age Cohort	Subject	Preferred Term	Onset*	Severity Grade	Related?	Outcome
QIV	18-64 yrs	283-0041	Road traffic accident	[redacted]	3	No	Fatal
QIV	18-64 yrs	297-0028	Asthma	16	3	Yes	Resolved

Arm	Age Cohort	Subject	Preferred Term	Onset*	Severity Grade	Related?	Outcome
QIV	18-64 yrs	299-0114	Chronic obstructive pulmonary ds	27	2	No	Resolved
QIV	≥65 yrs	287-0127	1-Atrial fibrillation	14	1	No	Resolved
			2-Post procedural hematoma	13	2	No	Resolved
QIV	≥65 yrs	292-0079	Myocardial infarction	6	3	No	Resolved
QIV	≥65 yrs	295-0055	Dehydration	27	3	No	Resolved
QIV	≥65 yrs	297-0055	Pneumonia	4	3	Yes	Fatal
QIV	≥65 yrs	298-0114	1-Acute pancreatitis	4	3	Yes	Resolved
			2-Hypoxia	9	2	Yes	Resolved
QIV	≥65 yrs	302-0139	Pyrexia	11	3	No	Resolved
TIV-1	18-64 yrs	289-0005	Atypical pneumonia	13	3	No	Resolved
TIV-1	≥65 yrs	306-0135	1-Renal impairment	19	3	No	Resolved
			2-O2 saturation decreased	18	3	No	Resolved
TIV-2	18-64 yrs	288-0028	Bipolar 1 disorder	4	3	No	Resolved

Source: Module 5, CSLCT-QIV-13-01 CSR Tables 12.3-2, 14.3.1.10.1, and 14.3.1.10.2, and electronic datasets.
QIV=Afluria QIV; TIV-1=Afluria TIV-1; TIV-2=Afluria TIV-2.
Onset = Number of days following vaccination
Severity Grade: 1=mild; 2=moderate; 3=severe
Related? : Yes signifies investigator's assessment of related to study vaccine. No signifies investigator assessment of not related to study vaccine.

- Subject 8400297-0028 was a 34 year old black/African American female smoker with multiple medical conditions including asthma (maintained on salbutamol and fluticasone inhalers), seasonal allergies, migraine headaches, type 2 diabetes, hypertension, gout, bilateral lower extremity edema, depression, anxiety, schizophrenia, chronic musculoskeletal pain, distal paraesthesias, anemia, and sickle cell trait. She stated that her asthma was well-controlled on medications, she had not been hospitalized in the year prior to vaccination, and had not received influenza vaccination in the past. Sixteen days following vaccination with Afluria QIV (Study Day 17), she had a severe acute asthmatic attack for which she was hospitalized. She responded to ipratropium bromide/albuterol sulfate inhalation treatments and intravenous methylprednisolone within 24 hours and resolved. The investigator assessed this SAE as possibly related to study vaccine but, alternatively, as possibly related to natural disease progression. The Applicant assessed this SAE as not related to study vaccine because of the prolonged duration between vaccination and the onset of symptoms. Additionally, the subject had symptoms of an upper respiratory infection, sore throat and runny nose, within the 16 day period between vaccination and onset of the asthmatic attack that may have triggered the exacerbation of asthma.

Reviewer comment: The reviewer agrees with the Applicant's assessment that this SAE was not likely related to Afluria QIV because an intercurrent viral illness is a more likely explanation for the exacerbation.

- Subject 8400298-0114 was an 84 year old white male with a history of prostate cancer, hypertension, hyperlipidemia, a vasodepressive syndrome with hypotension and syncope, degenerative joint disease, and seasonal allergies, who last received influenza vaccine in December 2013. On August 9, 2014, he fell on his abdomen. He was vaccinated with Afluria QIV on August 19, 2014. Four days later, he awoke with severe epigastric pain and was hospitalized with acute pancreatitis, elevated lipase, and no evidence of gallstones or dilated bile ducts. No ecchymosis or hematoma where the patient had fallen was found on

examination. The patient was not known to abuse alcohol. His course was complicated by low grade fever, paroxysmal atrial fibrillation, pleural effusions, hypoxia, and renal insufficiency, but he recovered with appropriate medications and supportive care, and was discharged home on August 31, 2014.

Reviewer comment: The investigator assessed the etiology of this patient's pancreatitis as most likely related to the trauma of falling flat on his abdomen or possibly to hydrochlorothiazide, but could not exclude a relationship to the study vaccine. The Applicant assessed the event as possibly related due to the temporal relationship, but noted a lack of biologic plausibility and cited other potential causes. These included increased risk associated with hyperlipidemia, medications (hydrochlorothiazide, simvastatin, losartan, and aspirin), and, possibly, increased parathyroid hormone associated with metastatic prostate cancer. Additionally, 10%-30% of cases of acute pancreatitis are idiopathic, some of which may be due to microlithiasis not detected on radiographic imaging.

To further investigate this event, the Applicant conducted a review of the entire CSL influenza vaccine safety database and found 4 reports of pancreatitis. Two were SAEs assessed as unrelated because they occurred 23 weeks post-vaccination in patients with histories of recurrent pancreatitis and alcohol abuse. The third was a postmarketing report of acute pancreatitis that occurred within 24 hours of vaccination in a 77 year old female with numerous serious co-morbidities but in whom no evidence of gallstones or history of alcohol use was reported. The fourth case was a postmarketing report in a 42 year old female who developed acute pancreatitis 20 days following receipt of influenza vaccine (brand unknown). Based on this information, the Applicant did not feel that this event represented a new risk associated with Seqirus IIV.

In accordance with the protocol, enrollment was halted pending DSMB review of this suspected unexpected serious adverse event (SUSAR). The DSMB Chair allowed the study to resume because, despite the temporal relationship:

- ***biologic plausibility was insufficient;***
- ***acute pancreatitis has not been previously associated with influenza vaccination;***
- ***the subject was on medications that have been associated with pancreatitis;***
- ***the subject was also at risk by virtue of hyperlipidemia and possibly prostate cancer; and***
- ***the Applicant's assessment of other similar reported events did not demonstrate a new risk.***

Although there appear to be more plausible explanations for the cause of this subject's acute pancreatitis, the temporal relationship to vaccination is strong and we will describe the event in the PI.

Reviewer comment: The reviewer evaluated the case narratives, case report forms, and electronic datasets for the other eight subjects who experienced SAEs from Day 1 through Day 28. Because of a lack of a strong temporal relationship, lack of biological plausibility, and/or alternative causal explanation, the reviewer agrees with the Applicant's assessment that these events were not related to the

study vaccines. As was noted for the fatal SAEs, there was a small imbalance in the proportion of subjects with non-fatal SAEs in recipients of Afluria QIV as compared to recipients of the TIV comparators. However, the majority of these events appeared unrelated to the study vaccines.

Non-fatal SAEs that occurred from Day 29 through Day 180 were reviewed. Because neither the Applicant nor the reviewer assessed these events as related to study vaccines, narratives of the non-fatal longer term SAEs are not provided in this review. Please refer to Section 6.1.12.3 for a discussion of deaths reported in the study.

Halting Rules

The protocol was halted on two occasions during the study, for Subject 8400298-0114 who experienced acute pancreatitis four days following vaccination with Afluria QIV, and for Subject 8400297-0028 who experienced severe asthma 16 days post-vaccination with Afluria QIV. In both cases, the DSMB Chair reviewed the event within 24 hours and determined that enrollment could proceed without a formal DSMB meeting. Please refer to the beginning of this section (6.1.12.4) for details of these SAEs and reviewer comments.

6.1.12.5 Adverse Events of Special Interest (AESI)

No AESIs were reported by the Applicant during this study (see Section 6.1.7 for definition and monitoring plan). However, one SAE was identified by the reviewer as an AESI. Subject ID 8400297-0082 was a 65 year old white male vaccinated with Afluria QIV on August 25, 2014 and diagnosed with a non-fatal SAE of granulomatosis and polyangiitis (Wegener's granulomatosis) on December 15, 2014, 113 days post-vaccination. The subject's past medical history included diverticulosis, squamous cell skin cancer, bilateral knee osteoarthritis and total knee replacements, bowel resection, deviated septum with septoplasty in 2009 and 2011, hypertension, and gout. He had also experienced sinus-related symptoms, including sinusitis, for three to four years prior to vaccination. Symptoms were unchanged between vaccination and the diagnosis which his physician reached on December 15, 2014. Oral prednisone and methotrexate were begun. The event was assessed as severe in intensity and serious (medically significant), and outcome as not recovered at the end of the study period. The investigator and Applicant assessed this event as not related to study vaccine because symptoms had been present for years prior to vaccination and the subject's physician had just arrived at a diagnosis ~four months post-vaccination without any significant change in clinical status.

Reviewer comment: Although biological plausibility may exist for a relationship between the study vaccine and this AESI/SAE because vasculitis is identified as a potential class adverse event for inactivated influenza vaccines, and has also been reported following influenza infection, causality has not been proven. Because this event occurred almost four months post-vaccination and, according to the Applicant's report, signs and symptoms of severe vasculitis pre-existed and were unchanged, the reviewer agrees with the Applicant's assessment. Vasculitis is already described in Section 6.2 of the PI.

6.1.12.6 Clinical Test Results

No clinical safety laboratories were prospectively collected in this study. Any abnormal laboratories obtained in the evaluation of significant AEs and summarized in the case

narratives of SAEs are found in Sections 6.1.12.3 and 6.1.12.4. Evaluation of subject listings and electronic datasets revealed one significant vital sign abnormality of low blood pressure (BP) in Subject 8400292-0116 who had a baseline BP of 85/66, sitting, forty-five minutes prior to vaccination with bio CSL TIV-2. The subject did not have a repeat blood pressure recorded on the CRF, but the electronic datasets indicate that he had no adverse reactions during the 30 minute post-vaccination observation period. See Section 6.1.12.2, Solicited Systemic Adverse Events, for a discussion of fever post-vaccination.

6.1.12.7 Dropouts and/or Discontinuations

Overall, 2.8% of subjects discontinued the study, most were lost to follow-up (2.4%), and none were due to AEs. The dropout/discontinuation rates were low, similar across treatment groups, and should not have introduced significant bias or influenced the interpretation of safety results.

6.1.13 Study Summary and Conclusions

Immunogenicity Conclusions

Vaccination with Afluria QIV elicited an immune response that met the eight HI GMT and SCR co-primary endpoints and pre-specified non-inferiority criteria for adjusted GMT ratios and SCR differences for all four vaccine virus strains contained in the vaccine as compared to U.S.-licensed Afluria TIV-1 and Afluria TIV-2 containing the alternate B strain. Afluria QIV met non-inferiority criteria in the overall study population of adults ≥18 years of age (primary endpoint) and in within both age cohorts of adults 18 through 64 years and ≥65 years (secondary endpoints). Criteria for non-inferiority were that, for all four strains, the UB on the two-sided 95% CI for the GMT ratio TIV/QIV must not exceed 1.5 and the UB on the SCR difference TIV-QIV must not exceed 10%. CSLCT-QIV-13-01 was adequately powered to test the statistical hypotheses within both age cohorts and overall.

Afluria QIV elicited an immune response that met secondary HI GMT and SCR endpoints and pre-specified superiority criteria for adjusted GMT ratios and SCR differences for each B strain as compared to U.S.-licensed Afluria TIV-1 and TIV-2 containing the alternate B strain. Immunological superiority (defined as both a LB on the two-sided 95% CI for the GMT ratio QIV/ TIV of at least 1 and a LB on the two-sided 95% CI for the difference in SCRs for QIV minus TIV of greater than 0) was demonstrated within both age cohorts 18-64 years and ≥65 years and overall.

Analyses of secondary immunogenicity endpoints, pre- and post-vaccination GMTs, the percentage of subjects with post-vaccination (Day 21) HI titers ≥1:40, and SCRs showed that immune responses were similar between Afluria QIV and the two TIV comparators, overall and within each age cohort. Comparison of responses between age cohorts revealed lower proportions of adults ≥65 years with post-vaccination HI titers ≥1:40 against the B strains as compared to adults 18-64 years, and statistically significantly lower SCRs for all four vaccine virus strains in adults ≥65 years of age as compared to the younger age cohort. The pattern of lower responses to the B strain, both in young and elderly subjects, has been observed in immunogenicity studies of Afluria TIV and other inactivated influenza vaccines. The lower SCRs relative to % post-vaccination HI ≥1:40 observed in both age cohorts has also been noted in study populations with high rates of influenza vaccination in the previous 12 months and where influenza vaccination is universally recommended for all persons 6 months of age and older.[11]

Afluria QIV was non-inferior to Afluria TIV-1/TIV-2 in both male and female subgroup analyses. Secondary superiority and immunogenicity exploratory endpoints were also met in these subpopulations. While females showed a trend towards slightly higher pre- and post-vaccination GMTs, differences in immune responses between the sexes were not statistically significant.

Racial and ethnicity subgroup analyses indicated that most subjects in CSLCT-QIV-13-01 were white and non-Hispanic or Latino. For these subgroups, NI and superiority criteria were met for GMT ratios and SCR differences for each of the four vaccine virus strains in Afluria QIV relative to the TIV comparators. Sample sizes were too small to conduct meaningful NI or superiority analyses on other subgroups. Immunogenicity subgroup analyses showed higher post-vaccination HI GMTs and SCRs for the black/African American subgroup relative to the white subgroup and for Hispanic/Latinos relative to non-Hispanic/Latinos. Small sample sizes precluded meaningful analyses for other racial subgroups.

Safety Conclusions

Overall, all three study vaccines were well-tolerated with similar safety profiles. Discontinuation rates were low (2.8%), similar across treatment groups, and none were due to AEs.

Six subjects died during the study, five in the Afluria QIV group and one in the Afluria TIV-2 group. None appeared related to the study vaccines. A total of 89 SAEs (including deaths) were experienced by 66 subjects during the six month post-vaccination period, including 15 SAEs that occurred in 12 subjects within the 28 days post-vaccination. Overall, more recipients of Afluria QIV reported SAEs as compared to recipients of TIV-1 or TIV-2 (2.3% versus 1.6%, and 1.5%, respectively), and more subjects in the older age cohort ≥65 years experienced SAEs as compared to younger adults 18-64 years of age (3.0% versus 0.8%). In the reviewer's opinion, none of the SAEs appeared clearly related to the study vaccines, and no large imbalances or unusual patterns were identified.

Overall, rates, severity, and duration of local and systemic solicited AEs were similar between the quadrivalent and trivalent formulations and were not unusual for an inactivated influenza vaccine. A total of 37.4% and 28.4%, respectively, of all subjects in the Safety Population experienced solicited local and systemic adverse events following vaccinations, with similar rates across treatment groups. Slightly higher proportions of Afluria QIV recipients reported measured injection site erythema (4.2% vs 2.1%-2.5%) and induration/swelling (3.2% vs 1.6%-1.8%) as compared to recipients of TIV-1 and TIV-2, but rates were low overall. Fever was uncommon, 0.5%-0.9% across treatment and age groups. Most local and systemic reactions were mild to moderate in severity.

Due to concerns for a potential increase in local reactogenicity with the addition of a second B strain antigen to the formulation, monitoring of severe (Grade 3) induration/swelling, cellulitis-like reactions, and cellulitis at the injection site were pre-specified safety endpoints in CSLCT-QIV-13-01. Although the total number of subjects who experienced Grade 3 injection site induration/swelling in the study was relatively low (n=6/3449, 0.17%), there was an imbalance between severe injection site swelling in subjects treated with Afluria QIV (0.3%) as compared to recipients of Afluria TIV-1 or TIV-2 (0.06%). Whether this was due to chance alone or to greater reactogenicity

caused by an additional B strain antigen is not clear. Four of the six reactions occurred in the older age cohort. None were serious. Cellulitis and large injection site swelling are already described in Section 6.2 of the PI, and postmarketing surveillance for such reactions will continue following approval of Afluria QIV.

A total of 719 subjects (20.8%) reported unsolicited AEs in the 28 days following vaccination, with similar proportions across treatment groups. No unusual patterns or imbalances were identified.

Subpopulation analyses showed that a higher proportion of females reported solicited and unsolicited AEs as compared to males in all treatment groups, a trend towards lower proportions of blacks/African Americans who reported solicited local injection site reactions as compared to whites, and a trend towards more solicited local and systemic reactogenicity among Hispanics and Latinos as compared to non-Hispanics/Latinos.

7. INTEGRATED OVERVIEW OF EFFICACY

The application supporting licensure of Afluria Quadrivalent consisted of one study, integrated analyses of efficacy are not applicable.

8. INTEGRATED OVERVIEW OF SAFETY

The application supporting licensure of Afluria Quadrivalent consisted of one study, integrated analyses of safety are not applicable.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnant women were not eligible to enroll in study CSLCT-QIV-13-01 and no subjects became pregnant during the study. The Package Insert was in the process of being revised to comply with the new Pregnancy and Lactation Labeling Rule (PLLR) when this review was completed. The PLLR replaces former pregnancy categories with more detailed descriptions of risk and data. No animal or human clinical trial safety data for pregnant or breastfeeding females are currently available for Afluria QIV. Based on postmarketing experience with Afluria TIV and other inactivated influenza vaccines, no safety concerns have been identified. Vaccination is recommended in pregnant women because they are at greater risk for complications of influenza infection. Vaccination of pregnant women may also protect infants in the first six months of life before they are eligible for vaccination.

9.1.2 Use During Lactation

Please see Section 9.1.1.

9.1.3 Pediatric Use and PREA Considerations

Afluria TIV is approved in children and adolescents 5 years and older. Please see Section 2.5 for relevant regulatory history related to withdrawal of licensure in children 6 months to < 5 years due to increased postmarketing reports of febrile seizures and febrile events associated with the SH 2010 formulation of Afluria, and for interactions with the Pediatric Research Committee (PeRC) leading up to submission of the current

efficacy supplement for Afluria QIV. Due to concerns over pyrogenicity in children < 5 years of age, Seqirus conducted a small safety study (CSLCT-USF-10-69) of Afluria TIV in children 5 through 8 years of age concurrent with CSLCT-QIV-13-01. Because this study demonstrated acceptable safety including less pyrogenicity than in prior studies, CBER agreed that plans for a larger study of Afluria QIV in children 5 through 17 years of age (described below) could proceed.

Afluria QIV triggered the Pediatric Research Equity Act (PREA) because it contains a new active ingredient (a second influenza type B virus antigen). Accordingly, the submission included a Pediatric Study Plan (PSP), and requests for a partial waiver and deferral of pediatric studies. Studies in children from birth to < 6 months of age will be waived because Afluria QIV does not represent meaningful therapeutic benefit over initiating vaccination at 6 months of age and is not likely to be used in a substantial number of infants younger than 6 months (due to the immaturity of the neonatal immune system and interference from maternal antibodies). Assessments in two pediatric age groups are deferred because the product is ready for approval for use in adults and pediatric studies have not been completed. These postmarketing requirements (PMRs) and their associated timelines are as follows:

1. CSLCT-QIV-13-02, a prospective, phase 3, randomized, observer-blind, comparator-controlled, multicenter trial to evaluate the immunogenicity and safety of Afluria QIV versus a U.S.-licensed quadrivalent inactivated influenza vaccine in children and adolescents aged 5 through 17 years.
    a. Final protocol submission: July 31, 2015
    b. Study completion date: June 30, 2016
    c. Final report submission: December 31, 2016

2. CSLCT-QIV-13-03, a prospective, phase 3, randomized, observer-blind, comparator-controlled, multicenter trial to evaluate the immunogenicity and safety of Afluria QIV versus a U.S.-licensed quadrivalent inactivated influenza vaccine in children aged 6 months through 4 years.
    a. Final protocol submission: July 31, 2016
    b. Study completion date: June 30, 2017
    c. Final report submission: December 31, 2017

The PeRC agreed with the Applicant's initial PSP, submitted to IND 15974, on September 3, 2014 and with the final PSP, submitted to STN 125254/565, on February 10, 2016.

9.1.4 Immunocompromised Patients

Information regarding the safety and effectiveness of Afluria QIV in immunocompromised individuals is not sufficient to support specific recommendations in this population.

9.1.5 Geriatric Use

The immunogenicity and safety data support licensure of Afluria QIV for use in adults ≥65 years. Please see Sections 6, 10, and 11 of this review.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Please see the clinical review of STN 125254/511 for results of a clinical study that demonstrated non-inferior immune responses in adults 18 through 64 years of age immunized with Afluria TIV administered by the PharmaJet® Stratis® Needle-Free Injection System (jet injector) as compared to needle and syringe, and supported the approval of administration of Afluria TIV by jet injector (JI) in this age group. In an April 21, 2015 pre-BLA meeting with the Applicant, CBER agreed that data submitted to support Afluria QIV would likely be sufficient to support administration via JI in adults 18 through 64 years of age, but that our final decision would depend on review of the data. In this reviewer's opinion, it is reasonable to extrapolate the data supporting the use of Afluria TIV to the QIV formulation and anticipate that the immunogenicity of Afluria QIV administered via JI in adults 18-64 years of age will be non-inferior to administration via needle and syringe. It is also reasonable to anticipate that the slightly increased local reactogenicity associated with Afluria QIV as compared to TIV may be further increased by administration via the PJ Stratis device, but the overall risk of severe reactions appears low based on data from CSLCT-QIV-13-01.

10. CONCLUSIONS

The immunogenicity and safety data from CSLCT-QIV-13-01 submitted to this efficacy supplement support traditional approval of Afluria QIV for use in adults 18 years and older.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 21: Risk Benefit Considerations – Afluria Quadrivalent		
Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition	• Influenza causes annual epidemics affecting ~5-20% of the population each year. Due to frequent mutations and reassortment, antigenic drift and shift, in viral envelope glycoproteins (HA and NA), the extent and severity of seasonal epidemics are variable and unpredictable. • In the US, annual influenza-associated respiratory and circulatory mortality rates ranged from 3,349 to 48,614 (average 23,607) from 1976-2007. Hospitalizations ranged from 55,000 to 431,000. Complications disproportionately affect persons < 2 years and ≥65 years of age and persons with underlying cardiac, respiratory, metabolic, or immune compromising medical conditions. The CDC estimates that 80%-90% of all seasonal influenza-related deaths and 50%-70% of hospitalizations occur in persons ≥65 years. However, antigenic shifts may cause pandemics that also result in significant mortality among healthy children and young adults. • Since 1985, two genetically distinct B virus lineages have co-circulated and comprise ~ 25% of isolates in the US. During the ten seasons from 2001-2002 through 2010-2011, prediction of which B lineage would predominate was correct for only five seasons, resulting in a mismatch between the vaccine and the circulating strain for 50% of the 10 year period. The CDC estimated that in a season where there is a B strain mismatch, the availability of a quadrivalent influenza vaccine could result in an annual reduction of 2,200-970,000 influenza cases, 14-8,200 hospitalizations, and 1-485 deaths.	• Influenza is a serious, sometimes life-threatening disease. Persons of all ages are at risk for significant morbidity and mortality. • Protection requires annual vaccination with a formulation containing virus strains predicted to circulate during each season. • Influenza B causes ~25% of the overall influenza disease burden. Deaths and hospitalizations due to complications of influenza B infection appear lower than for A/H3N2 but higher than for seasonal A/H1N1, and the majority of these complications occur in adults ≥65 years. Thus, vaccine coverage of both B strains is desirable, in both adults and in young children who also experience severe disease and high mortality due to B strains (34% of 309 deaths reported to the CDC during 2004-2008 were due to influenza B). • In 2013, the World Health Organization and VRBPAC recommended inclusion of a second influenza B antigen in quadrivalent influenza vaccines to provide coverage of both B lineages concurrently.
Unmet Medical Need	• Five antiviral agents are licensed in the US for the treatment or prevention of influenza in persons with severe, complicated, or progressive disease, or at higher risk for complications. Two adamantane agents are active only against influenza A and are no longer recommended because of widespread resistance. Neuraminidase inhibitors are also limited by emergence of resistance (primarily to type A viruses) and adverse reactions. • Licensed influenza vaccines available in the United States (2015-2016 season) include: six trivalent (Afluria, Fluarix, FluLaval, Fluviron, Fluzone, and Flucelvax) and four quadrivalent (Fluarix, FluLaval, Fluzone, and Fluzone intradermal) inactivated influenza vaccines (TIV and QIV), a trivalent recombinant influenza vaccine (Flublok), and a quadrivalent live-attenuated influenza vaccine (LAIV, FluMist). To improve immunogenicity, one high dose TIV (Fluzone HD) and one adjuvanted TIV (Fluad) are also licensed in the elderly. • Approximately 148 million doses of influenza vaccine were distributed in the US in the 2014-2015 season. Influenza vaccine coverage rates are relatively stagnant and remain below the DHHS Healthy People 2020 targets of 80% in persons 6 months through 64 years of age and 90% in persons ≥65 years of age. Although this does not appear to be due to a shortage of vaccine, the doses of vaccine distributed for the 2014-2015 influenza season are less than the population for whom the vaccine is indicated.	• Immunoprophylaxis is the preferred method of controlling influenza. The ACIP recommends annual influenza immunization for all persons ≥6 mos of age with no contraindications to vaccination. • Antivirals are important adjuncts for treatment and prevention of influenza but are not substitutes for vaccination. • Currently licensed influenza vaccines are effective against antigenically matched strains, and are well tolerated. When vaccine and circulating viruses are well-matched, vaccination with TIV is ~70-90% effective in preventing influenza illness among young healthy adults < 65 years of age. • Inclusion of both B lineages as part of a quadrivalent vaccine is projected to provide additional benefit in most seasons and is likely to become the standard of care. • An additional licensed QIV will be beneficial given the transition from TIV to QIVs and coverage targets.

Clinical Benefit	• In a randomized, controlled trial of 3449 adults ≥18 years, vaccination with Afluria QIV elicited an immune response that met pre-specified HI GMT and SCR co-primary endpoints and success criteria for non-inferior GMT ratios and SCR differences for all four vaccine virus strains as compared to US licensed Afluria TIV-1 and Afluria TIV-2 containing the alternate B strain. Afluria QIV also met non-inferiority criteria in both age cohorts of adults 18 through 64 years and ≥65 years (secondary endpoints). Afluria QIV elicited an immune response that met pre-specified secondary endpoints and success criteria for superior GMT ratios and SCR differences for each B strain as compared to US licensed Afluria TIV-1 and TIV-2 containing the alternate B strain. • Subpopulation analyses demonstrated a trend towards higher immune responses among blacks vs whites and Hispanics/Latinos vs non-Hispanics/Latinos. • Clinical benefit was inferred from Afluria TIV, manufactured by the same process as QIV, and for which clinical efficacy has already been demonstrated (STN 125254.259).	• Non-inferior immunogenicity was demonstrated in adults and elderly adults in an appropriately designed immunogenicity trial. • Immunogenicity results suggest that Afluria QIV is likely to confer protection against influenza similar to Afluria TIV for the strains common to both vaccines, and additional protection against the alternate B strain as compared to the trivalent formulation. Because Afluria QIV is manufactured by the same process as Afluria TIV and has demonstrated non-inferior immunogenicity and comparable safely, a clinical endpoint study to confirm clinical benefit is not necessary. • Subpopulation analyses represent trends but do not allow definitive conclusions.
Risk	• The most common adverse events (AEs) following vaccination with Afluria QIV were mild to moderate local injection site pain, muscle aches, and headache. Adults ≥65 years of age reported less reactogenicity than younger subjects. Most events resolved within 3 days. • Rates of solicited AEs in recipients of Afluria QIV as compared to TIV were similar except for slightly higher rates of severe events reported in the QIV group. Most notable was the difference in the rates of severe injection site swelling, 0.3% vs 0.06% among QIV vs TIV-1/TIV-2 recipients, respectively. Overall, rates of severe events were low, non-serious, and self-limited. • No other unusual AEs or trends were observed in adults ≥18 years of age. • Subpopulation analyses showed a trend towards more solicited and unsolicited AEs in females vs males, more local injection site reactions in whites vs blacks, and more local and systemic reactogenicity in Hispanics/Latinos vs non-Hispanics/Latinos. • A previous clinical trial comparing administration of Afluria (TIV) by the PharmaJet Stratis Needle-Free Jet Injector (JI) vs needle and syringe (NS) demonstrated non-inferior immunogenicity and greater local injection site reactogenicity associated with administration by JI. Administration of Afluria QIV by JI has not been studied. • Significantly more subjects vaccinated by JI in PJ-501-12-2 had a negative immunization experience (primarily injection site pain), and stated that they would not choose this mode of administration again as compared to subjects vaccinated by NS (27.3% vs 2.6%). • Safety was not evaluated in pregnant women or nursing mothers.	• Reactogenicity associated with Afluria QIV is acceptable and comparable to Afluria TIV. The safety profile of Afluria QIV with respect to unsolicited and serious AEs appears comparable to other US licensed TIVs and QIVs. • Subpopulation analyses represent trends to explore further but do not allow definitive conclusions. • Based on previous human experience, it is reasonable to expect administration of Afluria QIV by the PJ Stratis device to elicit an immune response comparable to administration by NS. • The slightly increased local reactogenicity associated with Afluria QIV as compared to TIV may be further increased by administration via the PJ Stratis device. • Inactivated influenza vaccines have a long history of safety and are recommended in pregnant females.
Risk Management	• The potential for increased local and systemic reactogenicity associated with Afluria QIV can be further described in postmarketing surveillance. • The clinical review team and OBE/DE determined that a neither a safety PMR, REMS nor a Black Box warning are required for Afluria QIV. • It is not clear whether the pregnancy registry or VAMPSS for Afluria QIV will occur by extension of the current postmarketing study for Afluria TIV vs an independent study.	• The known safety profile of Afluria QIV will be described in the package insert. • Please see the OBE/DE review for details of the postmarketing pregnancy study. • Risk management can be adequately addressed by describing the safety results from PJ-501-12-2 in the package insert without the need for a PMR, REMS, or Black Box warning.

11.2 Risk-Benefit Summary and Assessment

Afluria TIV has demonstrated clinical efficacy in adults 18-49 years (ATN 125254.259). Afluria QIV demonstrated non-inferior immunogenicity to in comparison to trivalent formulations of Afluria in both adults and elderly adults, suggesting that it is likely to confer protection similar to Afluria TIV for the strains common to both vaccines, and additional protection against the alternate B strain as compared to the trivalent formulation. The lower immune responses elicited in elderly subjects relative to adults 18-64 years, particularly against the influenza B vaccine antigens have also been observed in studies of other IIVs. Because Afluria QIV is manufactured by the same process as Afluria TIV and has demonstrated non-inferior immunogenicity, a clinical endpoint study to confirm clinical benefit is not necessary.

The safety data supporting licensure suggest slightly higher rates of severe local reactogenicity for Afluria QIV as compared to the trivalent formulations but the rates were very low and the events were non-serious and self-limited. Routine postmarketing surveillance for severe injection site reactions appears sufficient at this time. It is not yet clear whether the Applicant's decision to [redacted] in the manufacturing process will lower the risk of febrile reactogenicity, observed predominantly in children and associated with the SH 2010 formulation of Afluria TIV. As clinical trials of Afluria QIV proceed in children <9 years, we will recommend closer monitoring for febrile reactions and stringent halting rules.

Based on previous human experience, it is reasonable to expect administration of Afluria QIV by the PJ Stratis device to elicit an immune response comparable to administration by needle and syringe. The slightly increased local reactogenicity associated with Afluria QIV as compared to TIV may be further increased by administration via the PJ Stratis device but the overall risk of severe reactions appears low based on data from CSLCT-QIV-13-01.

11.3 Discussion of Regulatory Options

The Applicant has requested and the data support traditional approval of Afluria QIV in adults 18 years and older. Please see Section 11.1.

11.4 Recommendations on Regulatory Actions

From the clinical perspective, the data from CSLCT-QIV-13-01 support traditional approval of Afluria QIV in adults 18 years and older. Please see Section 11.1 for further discussion.

11.5 Labeling Review and Recommendations

Labeling negotiations were ongoing at the time this review was finalized. Major changes to the Applicant's draft new PI and areas of negotiation were:

- Highlights, Dosage and Administration [2], and Warnings and Precautions [5]: Removed dosage table; removed warning that safety and effectiveness have not been established in persons <18 years; removed warning that immune responses may be diminished in immunocompromised persons; removed statement that safety and effectiveness have not been established in pregnant women or nursing mothers.

- Adverse Reactions [6.1]: Added description of monitoring for severe injection site reactions and cellulitis.
- Postmarketing Experience [6.2]: Modified to be consistent with the Afluria (trivalent) labeling supplement (STN 125254.563).
- Pregnancy [8.1] and Lactation [8.2]: Modified to conform to the new PLLR.

Please refer to the final version of the PI, available in the EDR.

11.6 Recommendations on Postmarketing Actions

The Applicant submitted a Pharmacovigilance Plan (PVP) in Module 1 of the sBLA. Please see the OBE/DE review for a full discussion of the PVP and Section 9.1.3 for a discussion of pediatric PMRs.

It is not yet clear whether Seqirus has adequately identified and addressed the root cause of the SH 2010 increase in febrile seizures and events, predominantly in children less than 5 years, by , or whether an additional B virus strain will exacerbate this potential risk. Results of CSLCT-FLU-13-01 demonstrate a very small trend towards increased severe injection site swelling in recipients of Afluria QIV as compared to Afluria TIV-1 and TIV-2, however, the observed reactogenicity in the adult study was acceptable and no clear safety signal is identified. The review team agreed that risk management can be adequately addressed in the product labeling and through routine pharmacolvigilence activities by CBER and Seqirus. Additionally, clinical development will mitigate against potential risk in the pediatric population by proceeding sequentially from older to younger children, including sentinel subgroups with safety reviews by the DSMB, and employing stringent halting rules.

The Applicant will also continue routine monitoring of identified risks (hypersensitivity, anaphylaxis) and potential risks associated with influenza vaccination (encephalomyelitis, seizures/convulsions, Guillain-Barre syndrome, transverse myelitis, optic neuritis, Bell's palsy, and serum sickness). Additionally, safety in pregnant women exposed to Afluria QIV will be assessed by a pregnancy registry (please see the OBE/DE review for details).

OBE/DE does not recommend a PMR designed specifically to evaluate safety as a primary endpoint, a REMS, or a Black Box warning for administration of Afluria QIV. The clinical review team agreed with the OBE/DE recommendation.